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The Fifth Year of  
AUREOMYCIN


The Fifth Year of  
AUREOMYCIN

*Lederle*



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## INTRODUCTION

*It is now a little more than four years since aureomycin made its appearance, and in that brief space it has become established in the front rank of therapeutic agents. The first of the broad-spectrum antibiotics to be introduced, aureomycin has proved its value in an overwhelming literature, against an unrivaled range of infections of bacterial, rickettsial, viral, and unknown etiology.*

*Aureomycin may be confidently used in most infections. Specific sensitivity tests in vitro are rarely necessary and may be misleading, since many variables are capable of altering the results within wide limits. It is usually enough to determine the etiology of the infection, and if the organism belongs to a group against which aureomycin is active, it should be used.*

*Valuable as the antibiotics are, they cannot replace accurate diagnosis, therapeutic judgment, and skilled surgery. Focal infections must still be sought for and removed, collections of pus evacuated, and anatomic abnormalities corrected.*

*We shall endeavor in the succeeding pages to give an accurate picture of the status of aureomycin in medicine and surgery, as it appears at present. So much work has already been published as to make it probable that few surprises are in store for the reader. However, long-term results in chronic or recurrent diseases, such*

*as brucellosis, amebiasis, and syphilis, remain to be determined. Some of the rarer infections, and in particular the diseases peculiar to the tropics, are still being investigated. The published literature indicates that aureomycin is easily administered, well tolerated, and highly effective against a wider range of infection, according to present reports, than any other known antibiotic.*

*Because aureomycin is relatively nontoxic and fully effective by mouth, it may be readily used for patients treated in their homes. In patients unable to swallow or to retain food, high serum levels of aureomycin can rapidly be produced by intravenous administration. Because it diffuses into the cerebrospinal fluid, it is an effective drug in the treatment of meningitis caused by susceptible organisms. Because it reaches adequate concentrations in the urine, it is valuable in the treatment of urinary tract infections, especially against Gram-negative invaders. Aureomycin attains high concentrations in the bile, and is therefore an effective drug for use in certain types of liver and biliary tract infections. It has the two further advantages of rarely producing hypersensitivity in the patient, or drug resistance in the causative organism.*

*During the past two years, Lederle has devoted intensive efforts towards the purification of aureomycin, and has recently achieved a product so free from trace substances that it represents almost the ultimate in purity. This highly purified crystalline form, administered in divided doses with milk, seldom causes a gastrointestinal disturbance that will interfere with medication.*

*The new low minimum dosage for adults of four 250 mg. capsules daily, given at 4- or 6-hour intervals with milk, or other food, further insures excellent toleration.*

## INFECTIONS PRIMARILY INVOLVING THE RESPIRATORY SYSTEM

**A**UREOMYCIN, with its powerful action against an unprecedentedly wide assortment of bacteria and virus-like organisms, has proved to be of great value in infectious conditions affecting the upper respiratory tract, the anatomically-connected middle ear, and the bronchial and pulmonary tissues.<sup>76,78,87</sup>

Furstenberg<sup>45</sup> has commented upon the effectiveness of antibiotic therapy in acute otolaryngologic infections, the usefulness of aureomycin in permeating cell membranes, its lack of toxicity, and its capacity to penetrate the blood-brain barrier, protecting the patient against intracranial extension.

The etiologic diagnosis should, of course, be made whenever possible, but in all acute cases of respiratory system infection, it would seem advisable to begin aureomycin therapy at once without waiting for the results of extended determinations.

In chronic respiratory infection, less spectacular benefit will be obtained than in acute disease, since irreversible anatomic changes are likely to have taken place. Fibrosis will not only hinder contact of the drug with the pathogen; but, even in the event of the latter's complete eradication, some degree of permanent disability will remain. Passive congestion, accumulation of pools of secretion, and loss of tissue vitality are factors always to be considered in chronic respiratory disease.

## *Bronchiectasis*

Aureomycin has definite value in the long-term ambulatory management of bronchiectasis,<sup>118</sup> and in exacerbations of bronchiectasis associated with inactive tuberculosis.<sup>95</sup> Its wide antibacterial spectrum and relative freedom from undesirable effects, as well as the unlikelihood of its producing drug fastness in bacteria, combine to make it the drug of choice in this chronic condition, both for maintenance and also for the preparation of the patient for surgery.<sup>115</sup> Antibiotic therapy should be continued after operation for bronchiectasis until the patient has been afebrile for several days.

Martinitto<sup>80</sup> says that, in view of the tolerance to aureomycin shown by most patients, one may safely, when faced with any infection resistant to its current medication, make trial of 1 or 2 days of aureomycin therapy. He states that this is long enough to determine whether the reaction will be favorable or not, and that an agreeable surprise may result, as it did in 2 cases he described. One was that of a woman of 65, who since the age of 40 had suffered from bronchiectasis of both lung bases. At the time of beginning aureomycin, she was producing 150 to 400 cc. daily of foul, purulent secretion, often hemorrhagic. During the preceding 5 years, obvious secondary infection of the bronchial cavities had aggravated the condition. Every 15 or 20 days, she had a febrile episode with worsening of her general condition. Each attack was followed by an increase in cough, expectoration, dyspnea, and above all in emaciation. The last of these febrile episodes had lasted for more than 2 months, in spite of large doses of intramuscular and nebulized penicillin, intramuscular streptomycin, and other measures, including bronchial antiseptics, protein therapy, postural drainage, oxygen therapy, and cardio-tonics. Administration of aureomycin exerted an impressive effect. The quantity and the volume of sputum were reduced, the fever disappeared by the end of 24 hours, the general condition and the appetite improved. The author noticed stimulation of appetite by aureomycin on a number

of occasions. Aureomycin was continued for 12 days; during this period the patient visibly gained weight, ceased to cough or to have difficulty in breathing, and brought up no sputum whatever. One month after treatment had been stopped, the patient was continuing to improve generally and brought up only about 30 to 50 cc. of sputum a day. The treatment was repeated for 6 days and clinical normality was attained. The author noted that it will obviously be necessary to watch this patient for a time in order to determine the final degree of improvement.

Encouraged by this experience, Martinitto used the same procedure in another patient with bronchiectasis. In this patient, the infection in the bronchiectatic cavities had produced a septicemic picture, with frequent abundant and prolonged hemoptyses. One of these episodes was treated with 8 capsules, of 250 mg. of aureomycin each, daily for a period of 6 days. The volume of sputum diminished to one quarter, and there was no more hemoptysis. Dyspnea was much improved, without however completely disappearing. This patient was 50 years old and had had obstinate asthma since childhood. The author considers it advisable, in such cases, to give a course of treatment lasting 20 to 30 days.

### *Bronchiolitis and Bronchitis*

The acute bronchiolitis of infancy is characterized by peribronchial or patchy infiltration of the lungs, and is pathologically an interstitial pneumonia accompanied by atelectasis and emphysema. The etiology is unknown. It is possible that the disease may fall into the classification of the primary atypical pneumonias. Children with this condition often fail to respond to streptomycin, penicillin, or sulfonamides, but have shown response to aureomycin.<sup>104,108</sup>

Aureomycin has also been found to be effective in the broncho-bronchiolitis (suffocative catarrh) of elderly persons.<sup>81</sup>

Bronchitis or tracheobronchitis may be produced by a number of pathogens, bacterial and viral. In the adult, tracheobronchitis

most often occurs during the winter months, tends to become sub-acute or chronic, and may present a difficult therapeutic problem. In chronic cases treated by Kane and Finn,<sup>65</sup> penicillin and streptomycin were unable to control the infection, and were replaced by aureomycin. All of the 8 patients so treated were improved, the distressing cough either being markedly reduced or completely relieved. Fever disappeared in all cases in which it had been present. The work of Finland and co-workers<sup>10</sup> and of Whitlock and co-workers<sup>119</sup> has indicated that aureomycin is valuable in acute as well as in chronic cases.

If associated pyogenic infection, such as chronic bronchitis or bronchiectasis, is present in patients with asthma, antibiotic treatment frequently results in considerable relief of the underlying asthmatic condition. Barach<sup>6</sup> has observed this type of response in cases of chronic bronchitis associated with pulmonary emphysema or bronchial asthma, treated with aureomycin. Aureomycin was given to one such patient for 17 days with complete relief of cough and expectoration and definitely improved breathing. No adverse reaction to treatment was observed and there has been no recurrence for 2 years.

## *Empyema*

The treatment of empyema, hitherto predominantly surgical, is rapidly giving way to a combination of 2 or more of the following forms of therapy: closed aspiration and drainage, enzymatic debridement by means of VARIDASE\* Streptokinase-Streptodornase *Lederle* and aureomycin administration.<sup>23,69</sup> Although penicillin has been much used, aureomycin appears to be the antibiotic of choice in most cases, since it attacks all of the commonly found microorganisms, readily penetrates the lung tissues and enters the pleural fluid.

The combination of streptokinase-streptodornase and aureomycin has been successfully used by Tillett and co-workers.<sup>110,111</sup>

\*Reg. U. S. Pat. Off.



In 1 case of postpneumonic empyema due to pneumococcus type XXXIII, the infection failed to respond to sulfonamides, and later to aureomycin; even after 2 treatments with streptokinase-streptodornase. A third injection of the enzymes brought about a rapid drop in colony count; and rapid and permanent recovery followed the administration of aureomycin. The authors<sup>110</sup> interpret this prompt response as resulting from lysis of purulent material and fibrin, thus permitting readier access of aureomycin into the pleural cavity, and facilitating contact between the antibiotic and the infecting organisms.

Flippin and Israel<sup>41</sup> observe that the management of empyema has been revolutionized in recent years by the introduction of antibiotic therapy, streptodornase and surgical decortication; and conclude that there is no place for tube or open drainage in the present-day treatment of empyema.

The wide use of chemotherapy in respiratory infections may be expected to lessen the frequency of empyema. Once it has developed, the restoration of normal physiology and the removal of predisposing causes are of equal importance with direct attack on the localized infection.

In the prophylaxis or control of infection during operations on the lung, aureomycin would appear to be the antibiotic of choice. Postoperative pulmonary infections are caused, as a rule, by a mixture of Gram-positive and Gram-negative bacteria, against both of which aureomycin is active.

The development of empyema, often associated with bronchial fistula, is a very disturbing complication of total pneumonectomy, frequently requiring radical thoracoplasty. Kent<sup>66</sup> believes that the established concepts of surgical management need revision, since he and his associates have obtained very favorable results in a small series of 19 patients by the employment of a conservative regime with local instillation of antibiotics. He recommends the use of aureomycin. In 13 cases where the empyema was complicated by bronchial fistula, healing of the fistula took place after rib resection

and drainage. Eleven of this group were also cured of empyema by this means.

## *Influenza*

Although the effectiveness of aureomycin against the influenza virus has not been proven, it has been found frequently to bring about impressive symptomatic improvement, with return to normal temperatures and clearing of respiratory complications, in clinical influenza. It now appears to be the drug of choice in this disease. Impressive symptomatic improvement, regression of fever and clearing of pulmonary involvement usually begin within 36 hours.<sup>12,28,29,40</sup> In almost every case, the temperature returns to normal within about 48 hours. In the average patient with pneumonic involvement, the lungs become radiologically clear before the fifth day of treatment.

In a controlled study by Blocker and Numainville,<sup>12</sup> it was found that the duration of fever was much shorter in patients given aureomycin than in the control group or in patients receiving other antibiotics or sulfonamides.

A South African epidemic of influenza in 1950, while producing no fatal cases, caused much disability and affected about 20 per cent of the population. It came in 2 waves, the first of which responded to aureomycin, and the second to sulfadiazine. Cochrane and his colleagues<sup>27</sup> report that aureomycin was given to 100 cases, and reduced the febrile period from 4 or 5 days to less than 48 hours, in 70 per cent of the patients. Postinfluenzal depression was less severe than in control cases.

## *Laryngeal Infection*

Holinger, Johnston and Anison<sup>62</sup> have reported encouraging results in a small series of cases of laryngeal papilloma in children, when aureomycin was used in conjunction with surgical removal.

In discussing a later paper by Holinger<sup>61</sup> on papilloma of the larynx, Ullman<sup>113</sup> mentioned that, working with Pirquet, over a quarter-century ago, he had been able to demonstrate a virus in 3 of 5 cases of this condition.

Combe and co-workers<sup>30</sup> found aureomycin to be of real value in 2 cases of suffocative laryngitis in childhood, seen during an epidemic of influenza. Streptomycin was totally ineffective and penicillin only relatively active.

Schrack<sup>102</sup> has reported cure within 2 days, in 1 case of laryngitis with fever and malaise.

Wannamaker and co-workers<sup>117</sup> recently found that both penicillin and aureomycin shortened the duration of fever and of physical signs and symptoms, in a large controlled series of cases of pharyngitis and tonsillitis, aureomycin being somewhat more effective than penicillin. Early institution of treatment further improved results. Seven patients, 5 in the control group and 2 in the penicillin group, later developed rheumatic fever.

Segre<sup>103</sup> has reported 2 cases of chronic catarrhal laryngitis complicating brucellosis, which disappeared after an intensive course of treatment with aureomycin.

Healing was prompt in 16 cases of acute pharyngitis and 4 cases of pharyngolaryngitis, treated by Bablik<sup>4</sup> with topical aureomycin. This group included patients who had suffered from recurrent laryngitis for years and had never been completely free from discomfort or pain, even in the intervals. Subjective symptoms disappeared in a few days and the breath was cleaner than it had been for years. One of the patients was confined to bed with an acute pharyngitis accompanied by abscess formation and edema of the gum and of the uvula. After 48 hours, the pharyngitis had cleared, the abscess had spontaneously emptied and the edema had subsided. Aureomycin was also given to 8 cases of wound infection following tonsillectomy, remarkable benefit being obtained from its local use. The temperature dropped within 24 hours to normal, inflammation and swelling of the lymph nodes subsided

and the tonsillar fossae became clean-looking and began to granulate. Particularly striking was the result in 2 patients with fistulae following total extirpation of a neoplasm. Administration of penicillin and local treatment had no effect, but within 5 and 6 days after the beginning of aureomycin therapy, the fistulae had closed. In 1 case, aureomycin was discontinued after a short time; and 24 hours later the fistula opened again. Resumption of aureomycin closed it once more, within 2 days. Bablik points out that as a rule the healing of such a lesion requires several weeks.

The removal of a squamous epithelioma of the epiglottic region, by an extension of total laryngectomy was greatly facilitated by the preoperative use of aureomycin, as reported by Jacob and Masserann.<sup>63</sup> Objective signs had been confusing because of the local invasiveness of the tumor and the severe inflammation surrounding it. After 4 days of antibiotic treatment, there was no longer any infiltration of the pre-epiglottic mucosa, and the lesion could be clearly visualized. Operation was associated with X-ray treatment, before and after surgery. The patient was up on the third day after operation, and felt well and was able to swallow a week after operation.

## *Laryngotracheobronchitis* (Croup)

In the highly dangerous acute laryngotracheobronchitis of infancy, aureomycin has been shown to be effective as a therapeutic adjunct.<sup>5,38,39,48</sup> Awareness of this disease as a clinical entity is comparatively recent, and it has frequently been labeled bronchitis, tracheitis, pneumonitis or laryngitis, or even "common cold." Edema of the respiratory mucosa and viscous purulent exudation combine to produce critical interference with breathing, and may develop with alarming rapidity. Toxemia, dehydration and exhaustion contribute to the grave clinical picture. The infection may, of course, be a mild one throughout, but there is always

present the possibility of a sudden transition into the severely obstructive form. Over 80 per cent of the deaths occur in children less than 4 years old, and the younger the patient, the poorer is the prognosis.

In mild cases, antibiotic therapy may be all that is required, but in many patients tracheotomy may be necessary, followed by repeated bronchial suction, and by measures designed to humidify the atmosphere. Administration of aureomycin and relief of dehydration are indicated. In view of the mixed nature of this extremely serious infection and its resistance to treatment, immediate administration of a combination of penicillin, streptomycin and aureomycin has been suggested.<sup>38</sup>

The mortality rate in 202 cases of acute laryngotracheobronchitis studied by Berry<sup>9</sup> over a 5-year period, ending January 1949, was 13.8 per cent. The group included mild as well as severe infections and the mortality rate of the 47 severe cases was 50.5 per cent. After correcting these figures by the omission of patients dying within 8 hours of admission to the hospital, the over-all mortality was 5.8 per cent and that in severe cases 25.5 per cent. The high mortality in children less than 3 years of age is a reflection of the fact that the highest incidence of the disease occurs in this group. The actual mortality rate per year of age shows the highest figures between 8 and 9 years of age, the next highest between 4 and 5, and the third highest between 6 and 7. The most important single therapeutic measure is the provision of sufficient moisture. Oxygen alone is not indicated, since it acts as a drying agent. An excellent method of supplying both oxygen and moisture is the oxygen tent with humidity control. The mechanical humidifier is a great advance over the steam tent. Sedatives are generally considered to be contraindicated, but Berry<sup>9</sup> remarked that, at the Willard Parker Hospital, the use of whiskey in a dose of 1 dram per year of age to a maximum of 4 drams had beneficial effects, without producing apparent respiratory depression. As an instance of the effect of aureomycin in acute laryngotracheobronchitis, he

cites the case of a one-year-old infant who appeared to be dying, in spite of intensive treatment for 96 hours with penicillin, sulfonamides, streptomycin, supportive therapy and tracheotomy. He was finally given aureomycin parenterally. After 30 hours, remarkable improvement had occurred and his temperature was normal. Uneventful recovery followed, aureomycin being given for 10 days more. This is the only case, apparently, which has so far been treated at this hospital with aureomycin; but Berry<sup>9</sup> considers the result to be highly encouraging. He advocates immediate tracheotomy for all cases of acute epiglottitis. Of 7 children with acute epiglottitis seen in the series above, all died within 7 hours after admission to the hospital, the average length of survival being 2 hours.

A small epidemic of laryngotracheitis and laryngotracheobronchitis occurred in 1950 in Dundee, Scotland. Acute laryngeal obstruction was present in all of the childhood cases, while in adults the main complaint was a sore throat with a slightly reddened, granular pharynx. Other members of the child's family often had a similar infection and septic tonsillitis frequently developed. Sulfonamides were effective in relieving sepsis, but not pain. Forfar and co-workers,<sup>43</sup> who report this epidemic, drew attention to the fact that even if obvious cyanosis were not present, the ashen pallor that appeared in severe cases had a grave significance. It was not relieved by tracheotomy. They feel that conservative treatment as used by them (including chemotherapy, antibiotics and supportive treatment) has been justified by its results and that improvement did not follow tracheotomy, or laryngeal intubation, while laryngoscopy seemed to increase the respiratory distress. Nine cases were classified as severe, of whom 4 died. Of the 5 severe nonfatal cases, one was given penicillin and a sulfonamide while the others were given aureomycin as well. Two of the patients to whom aureomycin was given were so extremely ill that they had seemed unlikely to recover.

## *Lung Abscess*

Modern chemotherapy, especially the use of aureomycin and penicillin for bacterial infection and of streptomycin for tuberculous infection, has revolutionized the treatment and completely changed the prognosis of suppurative processes in the lung. Aureomycin has given noteworthy results.

Open drainage of acute lung abscesses and resection of chronic ones have produced a marked reduction in the mortality of pulmonary infection.<sup>83</sup> It is probable that the record will improve further as aureomycin comes to be more frequently used in the preparation of the patient.<sup>57</sup> In acute cases, its use tends to decrease the frequency with which operative intervention becomes necessary, and to aid in solving the difficult therapeutic problem presented by multiple lung abscesses.<sup>21, 25, 53, 57, 86, 101, 102</sup>

Gans and Potts<sup>47</sup> have described purulent infection in an anomalous pulmonary lobe with a fistulous opening into the esophagus. Following esophagoscopy, the patient was given a blood transfusion, penicillin and streptomycin. While on this therapy, an attack of high fever and dyspnea occurred, which subsided only when aureomycin was added to the medication. The anomalous lung was later successfully removed and the fistulous communication closed.

Sullivan and Bailey<sup>107</sup> indicate the importance of considering the possibility of amebiasis in any case of lung abscess, since pulmonary amebiasis may be present in patients without other evidence of this disease. They report 4 such cases which came under their observation in less than 18 months in 1 military hospital in the United States. They consider both emetine and aureomycin specific, and state that the toxicity of each is slight. They believe, therefore, that a therapeutic trial should be made with emetine, or aureomycin, in pulmonary abscess, before surgery is undertaken. As a purely diagnostic agent, emetine is perhaps preferable since it is active only against the ameba, but aureomycin is of therapeutic value since it also attacks secondary invaders. They describe 1 case

of amebic abscess of the lung, with pneumonic infiltration of the right middle and lower lobes and pleural effusion, which responded promptly to aureomycin. The patient was afebrile and his general condition improved within 24 hours. Ten days after beginning aureomycin, the cavity had shrunk 50 per cent. Aureomycin was discontinued after 19 days' administration, the cavity at that time being very small, and treatment was concluded by a course of emetine. An X-ray film taken 6 months later showed no evidence of disease.

Brocard and co-workers<sup>21</sup> note that today the cure of pulmonary abscess by an antibiotic is an everyday occurrence. However, they present 1 case which they regard as unusual and instructive, particularly since it underlines the necessity for bacteriological study, in order to select the best antibiotic for a given infection. This was the case of a young man who developed lung abscess after an attack of pneumonia and who did not respond to sulfonamides, penicillin or streptomycin. In spite of treatment, severe dyspnea and high fever continued, and the pathologic process in the lung continued to extend rapidly, until almost all of the right lung and about half of the left lung were opaque to X-rays. Death appeared imminent when the patient was transferred to the authors' service. Sputum examination revealed a staphylococcus and a pneumococcus, both of which were found to be resistant to penicillin, but extremely sensitive to aureomycin. The sensitivities to streptomycin and chloromycetin lay between these limits, except that the staphylococcus was insensitive to streptomycin. In view of the gravity of the patient's condition, both aureomycin and chloromycetin were added to the penicillin therapy. The condition improved rapidly and X-rays showed extensive resolution. In view of the results of the sensitivity tests, it was believed that the response was chiefly due to aureomycin, particularly since 4 weeks later the staphylococcus had lost 50 per cent of its sensitivity to chloromycetin and the pneumococcus was no longer sensitive to streptomycin. X-rays taken a few days later showed



little or no pulmonary pathology, and the temperature was normal. At a check-up examination 4 months after the institution of aureomycin therapy, the patient had no symptoms, either functional or general, and no pulmonary lesion was demonstrable by X-ray.

Cough, chest pain, dyspnea, and swelling of the neck developed rapidly in a two-year-old child who had accidentally aspirated a peanut.<sup>18</sup> On admission the child was acutely ill and was suffering from obstructive emphysema of the right lung and subcutaneous emphysema of the neck, left axilla and left side of the chest. The temperature on admission was 102.2°. The peanut, which was surrounded with purulent material, was removed by bronchoscopic aspiration and the child was given aureomycin and penicillin. Recovery was complete within 1 week.

Verhagen<sup>114</sup> obtained cure in a large lung abscess, resulting from embolism during puerperal sepsis. The pus contained *E. coli*, *B. proteus* and *S. viridans*. Penicillin and sulfonamide medication had no effect, but complete healing in 3 weeks followed the use of aureomycin (total 40 Gm. in 20 days).

Lobectomy was performed in a case of gangrenous abscess of the right upper lobe, as reported by Reboud and associates.<sup>90</sup> The patient had been ill for 10 months, with chest pain, cough, abundant foul expectoration, fever and anorexia, and had one severe hemoptysis. The condition was originally thought to be tuberculous. Some improvement followed the intramuscular and endobronchial use of penicillin, but the location of the lesion precluded postural drainage and, as was found at operation, sclerosis and stenosis of the bronchi hindered entrance of the antibiotic. Fever and expectoration could be controlled by aureomycin, but returned when it was discontinued. This fact and radiologic evidence of extension of the disease, led to the decision to operate. With preoperative aureomycin and postoperative penicillin, lobectomy was successfully performed. The patient gained 10 pounds in 3 weeks, at which time he was discharged as cured.

## *Otitis and Mastoiditis*

*Otitis Externa*—Acute external otitis and chronic suppurative external otitis are usually caused by Gram-negative bacteria, particularly *Ps. aeruginosa*, and by staphylococci. To be effective, medications should be applied in a water-soluble vehicle. In 28 patients with external otitis, reported by Wright,<sup>122</sup> cultures were made of the organisms and aureomycin was the only antibacterial agent with a consistent inhibitory effect, in high dilutions, on both *Ps. aeruginosa* and *Staph. albus*. Clinically, oral aureomycin was found to shorten the period of pain and swelling in severe acute otitis externa. In chronic suppurative cases, local use of aureomycin (or streptomycin) drops, plus frequent cleansing of the ear, appeared beneficial when other remedies failed. The best results appeared to be obtained by cleaning the ear thrice daily followed by dusting of the canal with aureomycin powder.

Bablik<sup>4</sup> has also found aureomycin of great value in acute diffuse forms of otitis externa, and has treated successfully a series of cases in this manner.

*Otitis Media and Mastoiditis*—Most cases of acute otitis media yield to modern conservative treatment. The incidence of acute mastoiditis and its complications has thus been reduced and the number of cases which become chronic has decreased. Antibiotics should be given in cases of fulminating otitis, and in all cases requiring paracentesis or showing any signs of extension beyond the middle ear.<sup>106</sup> If response to the antibiotic used does not follow in 48 hours, the therapy should be re-examined.

As a precaution against a later flare-up in the mastoid, adequate therapy must be given for a sufficient length of time to overcome the infection entirely; all cases should be kept under close observation for 72 hours after discontinuing treatment, and careful re-check should be made 1 month later.

Boies<sup>15</sup> is of the opinion that aureomycin will probably be found preferable to streptomycin in the treatment of acute middle

ear infections, particularly in those which are resistant to penicillin or sulfadiazine. He<sup>16</sup> estimates that, thanks to modern chemotherapy, the number of cases of chronic suppurative otitis media now requiring surgery is only a tenth of what it was about 15 years ago.

In the usual case of acute otitis media, before the days of chemotherapy, pulsation of the drum took 3 or 4 days to subside, and drainage lasted for 10 days to 2 weeks. Thunim<sup>109</sup> has reported a case of *Staphylococcus aureus hemolyticus* otitis in an adolescent girl, in which drainage after myringotomy had remained profuse for 2 weeks, notwithstanding full treatment with penicillin. After only 3 days of aureomycin therapy, resolution occurred, the canal becoming dry in 48 hours. The author believed this to be a definite specific response to aureomycin and not a coincidental spontaneous cure.

Complete subsidence of symptoms was noted by Schrick<sup>102</sup> in 2 cases of early catarrhal otitis media. One adult with purulent otitis did not respond and 1 child required combined therapy with penicillin, sulfadiazine and aureomycin. Both of these were chronic cases with an acute exacerbation provoked by swimming.

Whitlock and co-workers<sup>119</sup> have observed beneficial results with aureomycin in 1 case of mastoiditis; in 4 cases of chronic, and 4 cases of subacute, recurrent otitis media; as well as cure in 3 cases of acute purulent otitis. One case reported by them was that of a purulent draining otitis media of 2 months' duration, in a three-month-old infant. Staphylococci were cultured from one ear and *E. coli* from the other. Administration of 50 mg. of aureomycin every 6 hours stopped the discharge and healed the inflammation within 12 days. The child was discharged 2 days after the end of treatment and there had been no recurrence 1 month later. Three additional cases also obtained total remission. The effect of aureomycin is very striking in these chronic pyogenic aural infections, but surgery may be required for final cure.

Bertoye, Monnet and Collin<sup>10</sup> speak highly of the value of

aureomycin in the severe toxic and diarrheal conditions which are frequently associated with middle ear and mastoid infection during infancy. Seven of 13 gravely toxic infants had purulent otorrhea, usually bilateral. In addition to aureomycin therapy, paracentesis or antrotomy was practiced when indicated. In 6 of the 7 cases with otitis, cure resulted; the seventh child, who exhibited a severe hemorrhagic syndrome before treatment with aureomycin was begun, improved somewhat in general condition but died of generalized purpura. In the entire group of 13 patients treated with aureomycin, there were 3 deaths, while in a similar group comprising 9 infants, to whom aureomycin was not given, 5 died. Seven other infants, having auricular or auriculo-mastoid infections, not accompanied by a true toxic syndrome, also responded very satisfactorily to aureomycin.

Gans<sup>46</sup> was successful in treating a case of otitic herpes zoster with seventh nerve paralysis (Ramsey-Hunt syndrome) by means of aureomycin. He has since used this antibiotic, together with vitamin B complex, physiotherapy and iodides, in all cases of herpes zoster seen in the otolaryngology and ophthalmology departments, with gratifying results. Rapid control of the disease followed in 6 cases described in detail.

## *Pertussis*

The beneficial effects of aureomycin in pertussis have now been clearly demonstrated.<sup>8,19,82</sup> Infants, who are most seriously threatened by pertussis, are those who apparently are most favorably influenced. The earlier in the course of the disease aureomycin is given, the prompter and more complete are the effects; but in the majority of cases aureomycin decreases the frequency and intensity of the paroxysms, shortens the paroxysmal stage, and restores the well-being and appetite of the patient. Where definite and extensive lung involvement is present, combined use of aureomycin and penicillin has been recommended.<sup>7,90</sup> Prevention is still, however,

better than cure. Children who have received a complete course of active immunization rarely develop pertussis in a severe form, and even a partial course reduces the severity of the disease.

In spite of the improvement in the mortality statistics of whooping cough as a whole, the hospital death rate for patients less than 12 months of age is still between 5 and 10 per cent, and whooping cough causes more deaths in children under 2 years of age than any other acute infection except diarrhea or pneumonia. It should be observed that, until recently, infants less than 6 months old were not considered to be suitable candidates for immunization and therefore had no significant degree of protection against the disease.<sup>14</sup>

Rott<sup>93</sup> has found that, in order for streptomycin to be effective in pertussis, large enough doses must be given to arouse fear of possible toxic effects; but aureomycin, which to him appears the treatment of choice in the pulmonary complications of pertussis, can more surely and safely control the disease when administered in time, than was possible before.

Guélin<sup>54</sup> has reported the treatment with aureomycin of 24 young children with whooping cough. Twelve of the patients were less than 6 months old, 4 between 6 months and 1 year of age, and 8 between 1 and 2 years. Eight of the infants were gravely ill, but there were no fatalities. Fifteen of the children had uncomplicated pertussis; 5 had asphyxiating paroxysms (1 particularly severe case receiving both streptomycin and aureomycin); and 4 had pulmonary or otitic complications. Two of the children with complicated pertussis were given aureomycin alone, 1 aureomycin and streptomycin, and a fourth, aureomycin and penicillin. The first 3 children were aged 2 months or less, the fourth was 2 years of age. The 3 infants responded rapidly and completely to aureomycin, but the two-year-old child still suffered from rhinopharyngitis, and 20 days later developed bilateral otitis, which was cured by local treatment and a course of penicillin. Guélin found the action of aureomycin to be clear-cut in most cases, with diminu-

tion of the frequency and intensity of the paroxysms, and complete cessation of cough within 10 to 30 days. In 1 premature infant aged 1½ months, the severe and numerous coughing spasms disappeared completely in 48 hours, and in another child, the last cough was noted on the fifth day. He classifies the results of this series as one very good, 9 good, 2 average, 3 mediocre; there were no relapses. The 4 children with asphyxiating pertussis were given aureomycin alone. The asphyxiating character of the cough rapidly disappeared but the paroxysms themselves remained for about 18 days. In 1 twenty-day-old child, given aureomycin and streptomycin, the asphyxia disappeared on the third day, and there was no cough or vomiting after the tenth day, except for a few slight coughs several days later, when the child developed a cold. In the series as a whole, vomiting disappeared during the 4 or 5 initial days of treatment. It was noted that age appeared to influence the response to aureomycin, this response being most rapid and clear-cut in infants below the age of 6 months. Guélin found that the effect of aureomycin was not diminished by being given rather late in the illness, as long as it was administered not longer than 15 days after the onset of cough. He stresses the advantage of antibiotics such as aureomycin which can be given at home, thereby avoiding the risks of secondary infection which are always present in a hospital and tend to aggravate the whooping cough. He concluded that the use of aureomycin has brought about a considerable improvement in the prognosis of infantile whooping cough.

Agosto<sup>1</sup> gave aureomycin to 13 children with whooping cough. Results were good in 5, equivocal in 5, and absent in 3. The author felt that inability to retain the medication may have been a factor in lack of response. Among the children responding to aureomycin, those treated early showed the quickest favorable results.

Hensle,<sup>58</sup> reporting 25 pertussis patients treated with aureomycin, stated that in cases where treatment is begun in the first week of the paroxysmal stage, definite improvement follows within 5 or 6 days, and the patients appear to lose their infectious-

ness after a week. Miller and Ross<sup>82</sup> gave aureomycin to 6 patients with severe pertussis and with a poor prognosis. Three of the children were so ill that the outcome was doubtful, and in scarcely any would prompt recovery have been anticipated. However, within 2 weeks after the start of aureomycin, almost complete cure was the result. Cyanosis, fever and vomiting usually cleared within 5 days. Some of the patients had previously received other specific therapy, but the authors attributed the improvement noted in all these cases to aureomycin. Legros<sup>72,73</sup> has reported the satisfactory use of aureomycin aerosol in pulmonary infections, obtaining results equal to those of systemic therapy, but with much smaller doses. Lammers and Herold<sup>70</sup> noted that aureomycin aerosols produced a sustained reduction in the bacterial content of the sputum.

Booher and co-workers<sup>17</sup> found that, in 22 children with pertussis who were given aureomycin, there was a notable decrease in the duration of the paroxysmal stage, although the average duration of cough and the time in hospital were unchanged. Their results did not seem to be quite so favorable as those obtained by others, but they point out that no failures occurred. There were 2 failures in a group of 36 children treated with chloromycetin, and 3 among 31 children given terramycin. Seven other patients showed absolute refractoriness to every form of therapy, whether the drugs were given alone or in all possible combinations. In the other group of 5 cases given combinations of 2 of these 3 antibiotics, the standard dose of each being used simultaneously, there seemed to be no significant difference from the results obtained with a single drug—in fact, the whooping and coughing stages seemed to be somewhat lengthened. The authors used a slightly smaller daily dose of the antibiotic than had been used by other investigators. Streptomycin appeared to be of questionable clinical value. The authors observed indications that the pertussis organism may be developing an altered sensitivity to antibiotics.

All treatment, even that with aureomycin, is inadequate in certain very grave forms of pertussis of an asphyxiating and convul-

sive type, which often result in death. A particularly grave form is that characterized by fairly high temperature; violent and almost continuous cough, with severe dyspnea and prolonged apnea; marked cyanosis; motor crisis, more or less generalized, but without meningeal symptoms. In such cases of severe respiratory distress, relief has been obtained by removal of spinal fluid under manometric control. The apneic crisis is relieved, the fever falls by crisis and the respiratory rhythm becomes regular. The spinal fluid in these cases shows little that is distinctive, but the pressure is elevated (50 to 60 millimeters). Saccani<sup>34</sup> has used lumbar puncture in 8 such cases, ranging in age from 2 years to 8 years. He considers this procedure to be urgently indicated in the presence of severe dyspnea. In a little more than a week the patients were very much better, with attenuation both of the intensity and of the frequency of the cough. Aureomycin was given in 4 of the above 8 cases by mouth when possible, otherwise rectally. Saccani looks on lumbar puncture as a lifesaving measure, to be done immediately, and considers that for best results, it should be followed by the administration of aureomycin.

Dos Anjos<sup>36</sup> states that vitamin K given parenterally has proved valuable as an adjunct to other therapy, in both whooping cough and bronchial asthma.

A report from India, by Debdas,<sup>33</sup> deals with the results of aureomycin therapy in 10 cases of whooping cough. In every case, there was clear-cut clinical response, with decrease in the number and intensity of paroxysms after the second or third day and their complete disappearance by the end of 7 to 10 days; except in 1 case in which the cough did not completely disappear with 1 course of treatment. Bronchopneumonia which had been present in 1 case was cured; as was a chronic leg ulcer, which had previously resisted all forms of local treatment. Debdas states that aureomycin should be begun preferably in the incubation period or in the catarrhal stage, and treatment should be continued for about 10 days to prevent relapse.



In a report from Czechoslovakia, Dokulil<sup>35</sup> states that aureomycin gave very good results in 18 cases of whooping cough, particularly in the early stages, although even in late stages it often brought improvement.

While satisfactory clinical response has been observed following the use of terramycin in some patients with pertussis and bronchopneumonia, Sayer and co-workers<sup>97</sup> were forced to administer intravenous aureomycin to one severely ill two-year-old boy with an associated encephalitis, when his condition continued to deteriorate after 48 hours of oral terramycin. After 2 days, during which his condition remained stationary, he slowly improved on aureomycin therapy. They observed satisfactory clinical response to terramycin in 12 of 16 children with uncomplicated whooping cough, but in 2 infants with severe pertussis who did not improve after 6 days of treatment, gradual clinical improvement followed the substitution of aureomycin.

### *Pharyngitis and Tonsillitis*

*Pharyngitis*—In acute pharyngitis, whether exudate is present or not, aureomycin is highly effective. Schrick<sup>102</sup> treated 2 adults and 2 children with nonexudative pharyngitis, all of whom reported complete symptomatic recovery within 24 hours of beginning treatment. Finland and co-workers<sup>40</sup> reported quick response to aureomycin in 3 patients with streptococcal pharyngitis. Bertoye and co-workers<sup>10</sup> consider aureomycin to be of great value in the severe pharyngitis of young infants and observed immediate improvement in a four-day-old child.

Four cases of chronic throat infection reported by Lövgren<sup>77</sup> were suspected of being of viral origin. Articular rheumatism developed in these patients, but the throat inflammation disappeared after administration of 4 Gm. of aureomycin.

About 1 week after the end of therapy, the joint inflammation disappeared. Prior to treatment, these patients had a normal sedi-

mentation rate, a slight relative lymphocytosis and low serum iron values. Cerviá<sup>24</sup> also gave aureomycin to a patient with chronic rheumatic disease and frequent relapses, with resulting diminution of pain and regression of fever.

*Tonsillitis*—Aureomycin gives satisfactory results in acute tonsillitis. Harvey, Mirick and Schaub<sup>57</sup> have reported good response in 1 case where the infecting organism was *Streptococcus pyogenes*. In 2 of the 3 cases of pharyngitis reported above, there existed also exudative tonsillitis and cervical adenitis; and Finland and co-workers<sup>40</sup> noted that aureomycin brought about prompt improvement.

Whitlock and co-workers<sup>119</sup> obtained cure in all of 3 cases of acute tonsillopharyngitis by the use of oral aureomycin.

Twenty-six of 30 cases of exudative tonsillitis and pharyngitis, apparently of nonbacterial origin, treated by Schrick<sup>102</sup> with aureomycin, were improved and afebrile in 48 hours and completely well in 4 days. There were no complications in any case which received treatment in the early stage of illness. Schrick has found that aureomycin controls infection in chronically diseased tonsils and adenoids and thus permits their safe removal.

In 12 cases of tonsillitis and sore throat treated by Janbon and co-workers,<sup>64</sup> aureomycin produced normal temperatures in 24 to 48 hours. The earlier treatment was begun, the more rapidly did the disease subside.

## *Pneumonia*

It is no longer essential, although still highly desirable, to identify the causative organism in all cases of pulmonary infection, since aureomycin has been found effective in pneumonias of all types—bacterial, rickettsial, viral, and those of unknown etiology.<sup>50</sup> Its action in the coccal pneumonias compares favorably with that of penicillin, and there is much less chance of encountering a resistant organism. In Friedländer pneumonia, it is believed that aureomycin will replace streptomycin. It produces rapid improvement,

greatly lessening the tendency to the development of chronic infection with fibrosis or bronchiectasis, and has been reported as clearing up the multiple lung abscesses which not infrequently develop in this disease. In tularemia, even with severe pneumonic involvement, marked improvement usually takes place within 24 hours.<sup>89,121</sup>

The so-called primary atypical pneumonia, which is usually of viral etiology, shows almost uniform response to aureomycin within 12 to 72 hours.<sup>13,52</sup>

In the serious infections which may attack the newborn infant, and which frequently take the form of a highly fatal broncho-pneumonia, Ribadeau-Dumas,<sup>91</sup> Sarrouy,<sup>96</sup> and their associates, found the results obtained by aureomycin surpassed their hopes. The authors believe that, while in the less serious cases the classical treatment may be used, aureomycin, to which they assign first rank among chemotherapeutic agents, should be begun if improvement is not evident within 48 hours.

The tendency to abscess and cavity formation, which is a feature of staphylococcal or klebsiella pneumonia, makes pneumonia due to these organisms a particularly dangerous type of infection. While penicillin has hitherto been considered the antibiotic of choice for staphylococcal pneumonia, and streptomycin for klebsiella pneumonia, it seems probable that aureomycin will replace both these antibiotics. Gruber and co-workers<sup>53</sup> have presented a case of pneumonia caused by klebsiella in a thirteen-month-old boy, in which conjoint administration of streptomycin and aureomycin produced sterilization and closure of all cavities. Kirby and Coleman<sup>68</sup> also studied the effects of various antibiotics in 11 patients with Friedländer pneumonia, 8 of the patients being chronic alcoholics, and conclude that aureomycin is probably as effective as streptomycin in the treatment of this infection.

Chronic suppurative pneumonia, or lung abscess, may follow the acute stage of Friedländer's pneumonia, and may require

lobectomy or pneumonectomy. Since surgical intervention, even as long as 5 years after the acute infection, may reactivate the disease, the resistance of the organism should be determined pre-operatively and suitable antibiotic therapy instituted.

Young and associates<sup>123</sup> stated that most of the non-tuberculous pulmonary infections which will respond to streptomycin will respond in the same way to aureomycin or terramycin, so that it is rarely necessary to use streptomycin in pulmonary infections.

Kirby<sup>67</sup> has pointed out that the mortality rate from pneumonia has dropped more than 40 per cent from the average for the decade 1938-1947, undoubtedly as a result of the increasing employment of antibiotics. Striking as are the results with penicillin in pneumococcal pneumonia, he feels that aureomycin compares favorably with this antibiotic, and notes that the mortality rate following aureomycin was found by Dowling<sup>37</sup> to be less than one-third of that in penicillin-treated cases, in a series of 131 cases given aureomycin and 600 cases given penicillin.

Leland and Allebach<sup>74</sup> have recently made a comparison of the effect of aureomycin and of penicillin, in 2 series of unselected cases of bacterial pneumonia. Thirty-six were treated with penicillin and 40 with aureomycin. There was only 1 death, a patient with staphylococcal pneumonia treated with aureomycin. This patient had severely nephrosclerotic kidneys, was in uremia, and was considered unlikely to have responded to any form of treatment. While superficially there appeared in these series to be little difference in the therapeutic response to both agents, closer inspection suggests that the effect of aureomycin was the better. The average age of the patients in the aureomycin series was considerably higher than that in the penicillin series, 43 per cent of those treated with aureomycin being 60 years of age and over, while only 11 per cent of those treated with penicillin were in this age group. Furthermore, their illness had been of rather longer duration before admission and there was a higher percentage of severe underlying disease, and of bacteremia (9 bacteremias, including

3 staphylococcal bacteremias, in the aureomycin series; as against 4 in the penicillin series).

Flippin and co-workers,<sup>42</sup> in a recent comparison of the effectiveness of various antibiotics in bacterial pneumonias, concluded that treatment with aureomycin and chloromycetin gave approximately the same results as penicillin treatment, but the requisite dose with aureomycin was half that required for chloromycetin.

In 58 patients with pneumococcal pneumonia given aureomycin and 58 given penicillin, the results with aureomycin compared favorably with those following penicillin. Austrian and co-workers,<sup>3</sup> who report this study, state that the stimulation of intestinal motility by aureomycin may tend to lessen the tendency toward obstipation and abdominal distention, which has so frequently been reported as a distressing complication of lobar pneumonia. There were few toxic reactions or complications in either series. One death occurred in the aureomycin group and 2 in the penicillin group.

In a group of 39 cases of pneumonia in infants and children treated by Olshaker and associates,<sup>84</sup> 30 cases were bacterial in origin; the remaining 9 cases were considered to be of viral origin. In the former group, the results with aureomycin were good in 24 cases, fair in 5, and poor in only 1. Eight of the 9 cases of viral pneumonia were favorably, although less strikingly, affected by the drug. Anderson<sup>2</sup> gave aureomycin to 19 children with primary atypical pneumonia, who had been unimproved or who had become clinically worse during 2 to 3 days' treatment with sulfadiazine or penicillin or both. The clinical and roentgenologic response to aureomycin was marked in all cases and dramatic in some.

Of 60 children with acute lung infections treated by Gek<sup>49</sup> in Singapore, 45 were less than 6 months of age and few were over 1 year. In the first half of this series, penicillin and sulfonamides were given. If response failed to appear, aureomycin was substituted. As aureomycin became available in larger quantity, it

was given as soon as the diagnosis was made. In a previous series of 60 cases, given only penicillin and sulfonamides, there were 31 deaths; in 30 cases in which penicillin was first used unsuccessfully and then replaced by aureomycin, there were 8 deaths; and in 30 cases treated with aureomycin from the beginning, there were 10 deaths. The author considers that the recovery rate of 70 per cent in aureomycin-treated cases is a significant improvement on the 50 per cent recovery seen in penicillin-treated cases.

Mantero<sup>79</sup> believes that there is no doubt of the specificity of aureomycin against the virus of primary atypical pneumonia. He cites the case of a three-year-old girl, who was given aureomycin on the second day of pneumonia and was afebrile on the fourth day: in contrast to 2 other children in the same family, who had received either no aureomycin, or aureomycin very late in the course of the disease, and whose illness lasted more than 2 weeks.

de Font-Réaulx<sup>34</sup> points out the difficulty frequently encountered in diagnosing virus pneumonia in children, and describes 2 cases rather closely resembling primary tuberculous infection, 1 of them presenting a clinical picture which suggested lung abscess. He uses aureomycin as a therapeutic criterion for the diagnosis of this type of pneumonia, while awaiting results of the cold agglutinin test and of the Hirst reaction; that is to say, he considers as positive an immediate response, within less than 24 hours, to a dose of 3 Gm. of aureomycin.

He observed, what has so frequently been stressed by other workers, the comparatively good general condition of the majority of patients before treatment; and the slowness of response of the lung signs, in contrast to the rapidity with which the temperature and the subjective manifestations respond.

Corti and DiGuglielmo<sup>31</sup> reported a case of virus pneumonopathy, persisting for 9 months and absolutely refractory to penicillin, streptomycin and the sulfonamides. The infection responded promptly and completely to the administration of aureomycin. There was a slight relapse when aureomycin was discontinued, but

there was prompt response to a second course of the drug.

Sirchich and Rakovská<sup>105</sup> have used aureomycin with excellent results in 20 cases of primary atypical pneumonia in infants.

In a controlled study of virus pneumonia, Hilden and Norregaard<sup>60</sup> treated 13 adults with aureomycin. Penicillin and sulfonamide treatment had previously been tried without response. In all cases, administration of aureomycin was followed by prompt disappearance of fever, 12 of the patients being afebrile within 36 hours on the average. In untreated cases the average duration of the disease is about 37 days. Romske,<sup>82</sup> in discussing this paper, stated that he had similarly treated 13 cases with the same result, and that in some cases where the temperature remained subfebrile, it fell to normal when penicillin was given.

Pleural effusion complicating primary atypical pneumonia is extremely rare, but Billiottet and Ezanno<sup>11</sup> have reported 1 case. The patient was a three-and-a-half-year-old girl, with high fever and marked secondary anemia, who developed a hemorrhagic pleural effusion. Treatment with penicillin, streptomycin, vaccine and liver extract was completely ineffective. In the third week of her illness, aureomycin was administered; and, between the second and the fourth day, the temperature dropped to normal. Within less than 2 weeks the child was discharged, without any residual signs of effusion. Clinical, laboratory and radiologic tests 3 weeks later showed almost complete restoration to normal.

Sarrouy and co-workers<sup>96</sup> consider that in severe bronchopneumonia in infants, aureomycin should be given at once. In less serious cases, standard methods of treatment may be used but, if improvement is not evident within 48 hours, aureomycin should be begun without further delay. They observed excellent results with the use of this antibiotic in an epidemic of extremely severe influenzal bronchopneumonia among young infants in Algiers, during the winter of 1949-1950.

Diffuse interstitial fibrosis of the lung, a comparatively rare disease, apparently of virus origin, which progresses rapidly to

death, closely resembles pathologically the experimental influenzal pneumonia of animals. Brock<sup>22</sup> suggests that aureomycin may be life-saving in these cases.

The control of acute pulmonary infection by chemotherapy has thrown into prominence the degenerative conditions which produce chronic pulmonary disease. Gordon and his associates<sup>50</sup> have studied more than 100 men and women with pulmonary manifestations which were undoubtedly related to degenerative conditions of the lungs. They found that improved drainage of the bronchioles, resulting from the active movement of air in and out of the alveoli produced by the use of intermittent positive pressure breathing treatments (I P P B), together with a wetting agent and diaphragmatic elevation, provided an effective method of treatment. Antibiotics such as aureomycin were found to be effective in controlling recurrent nontuberculous infection.

### *Psittacosis (Ornithosis)*

Scadding<sup>98</sup> states that aureomycin appears to be curative in diseases of the psittacosis-ornithosis group, which manifest themselves principally as a pneumonitis, and should be used if available.

Psittacosis is contractable from birds of the parrot family and from sea gulls, and has a mortality rate of 30 to 40 per cent in man.<sup>44</sup> Aureomycin is considered to be the best available therapeutic agent.<sup>100,112</sup>

One case of psittacosis,<sup>71</sup> after failure to respond to a sulfonamide and penicillin, showed rapid improvement when a larger dose of penicillin was given together with aureomycin. Brainerd and co-workers<sup>20</sup> treated 3 cases of psittacosis, which had shown poor response to penicillin but which responded well to aureomycin. They believe the latter antibiotic to be the indicated remedy in this type of infection. Davis and Hawkins<sup>32</sup> gave aureomycin (14 Gm. in 5 days) to 1 case; beginning on the third day of illness. Recovery was prompt, with normal temperature 30



hours after the first dose. In a patient reported by Green,<sup>51</sup> who had suffered accidental exposure to psittacosis virus 5 days before the onset of illness, striking improvement took place after 48 hours of treatment with aureomycin, and within 24 hours in another patient reported by Hamke and Risse.<sup>56</sup>

Trüb<sup>112</sup> gave aureomycin to 7 patients with psittacosis, in an epidemic occurring in Germany during the winter of 1949-50. In all, an impressive clinical response was observed within 24 hours. Hamke and Risse,<sup>56</sup> referring to the same epidemic, reported that cases treated with aureomycin were afebrile within 24 hours.

Videla and Pandolfo<sup>116</sup> gave aureomycin intravenously to 6 grave cases of psittacosis, unable to take medication by mouth; and followed this with oral treatment as soon as the condition permitted. The result was spectacular, for within 24 to 48 hours of beginning treatment, the acute phase of the illness was ended.

Trüb<sup>112</sup> notes that psittacosis should be thought of in the differential diagnosis of atypical pneumonia, and that if the case appears to be one of this disease, the health officer should be notified. He states that the clinical results obtained indicate that aureomycin is the remedy of choice for the treatment of this infection.

Hamke<sup>55</sup> has reported 8 cases of psittacosis, transmitted by parrots. The course of the disease was moderately severe, or severe, in 6 patients, mild in the youngest patient, and fatal in 1 patient. Treatment with quinine and calcium in combination, and with sulfathiazole, penicillin and streptomycin failed. Three gravely ill patients, treated with aureomycin, had normal temperatures within 24 hours, and all recovered. The effect of the drug did not depend on the time of beginning treatment. The authors feel that aureomycin therapy is specific and greatly improves the prognosis.

The strain of ornithosis virus carried by pigeons produces a disease closely resembling psittacosis. Lépine,<sup>75</sup> pointing out that the vectors are different for both diseases, notes 2 clinical points of

differentiation. Pigeon ornithosis is not contracted from human cases of the disease, and its course is always benign; neither of these is true of parrot ornithosis. Lépine further speaks of the "spectacular efficacy" of aureomycin in cases of ornithosis.

Woodward<sup>120</sup> reported dramatic results from the administration of aureomycin, in a case of ornithosis contracted from pigeons and characterized by bilateral severe headache and toxemia.

### *Rhinitis and Sinusitis*

Antibiotic aerosols have proved disappointing for the treatment of nasal and sinus infections. The drug tends to be carried away by surface action and little penetrates into the infected tissues. Aureomycin, given by the oral route, is carried by the tissue fluids to the site where action is desired, penetrates the cell membranes and sets up an antibacterial action in the involved cells. The presence of excess mucus may retard both phagocytosis and antibiosis, hence it should be removed by lavage where possible. Fibrinous exudates may have the same effect and investigations upon the use of streptokinase-streptodornase solutions for their removal are under way. Chronic sinusitis is, of course, a symptom-complex, not simply an infection. Nutrition, endocrine balance and other factors play important roles in the etiology of this complex.

Prigal and Molomut<sup>88</sup> have studied the effect of various antibiotics on organisms isolated from the pharynx of patients with sinorespiratory infections. Aureomycin was found to be of great potency as compared with other antibiotics, and to be effective against the greatest number of strains isolated, only 1.8 per cent being completely insensitive. They stress the value of taking cultures and of making sensitivity tests, as a guide to the use of aerosols in sinorespiratory conditions, and advocate investigation of the possibility of a carrier state existing in the contacts of a patient with recurrent or chronic infection.

Peterson and Hadley,<sup>85</sup> conducted a study of aureomycin effec-

tiveness in the treatment of sinus infections, the invading organisms including *Staph. aureus* and *albus*, *Strep. hemolyticus* and *E. coli*. Nine acute infections cleared rapidly following the use of oral aureomycin, and appeared to be completely cured. Remarkable improvement, or complete recovery, took place in 9 chronic cases, several of which had previously been subjected to intensive medical and surgical treatment without effect. Harvey, Mirick and Schaub<sup>57</sup> also obtained satisfactory results in 6 patients with sinusitis. One child, reported by Schrick,<sup>102</sup> with rhinitis and sinusitis of 1 month's duration, responded favorably to aureomycin within 6 days. Whitlock and co-workers<sup>119</sup> obtained cure in 2 cases of acute purulent nasosinusitis and improvement in 1 chronic case, using aureomycin systemically.

Bablik<sup>4</sup> states that a number of patients in the early stages of an acute rhinitis were strikingly benefited by the introduction of aureomycin ointment into the nose several times a day.

Chen and Dienst<sup>26</sup> found oral aureomycin 2½ times as effective as antihistamines in relieving the symptoms of the common cold, and consider it the best cold remedy which we have at present. Laryngitis was cured in 24 to 48 hours, and bronchitis did not develop, as it did in patients given an antihistamine or a placebo.

## CHAPTER ONE

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## INFECTIONS PRIMARILY INVOLVING THE DIGESTIVE SYSTEM

AUREOMYCIN rapidly and effectively reduces the bacterial flora of the gastrointestinal tract, in doses which will not irritate the mucosa and thereby reduce its vitality. This antibiotic<sup>50,181</sup> exerts its highest effectiveness when taken by mouth, and small doses will simultaneously reduce the intestinal flora and provide therapeutic blood levels, protecting the patient against septicemia and peritonitis.<sup>144</sup> Amounts of antibiotic sufficient to procure complete sterility of the fecal content may injure the gut itself. It can hardly be too strongly emphasized that the aim of the surgeon is a smooth convalescence and not a sterile stool. It has been suggested<sup>48</sup> that the administration of an adsorbing antacid with aureomycin, for gastrointestinal infections, might produce higher or more prolonged local concentrations of the antibiotic.

### *Abscess*

*Appendiceal*—Yeager, Byerly and Holbrook<sup>181</sup> obtained excellent results with aureomycin in 2 cases of acute perforated appendicitis with a walled-off abscess. In both cases, the mass which could be felt in the abdomen decreased rapidly in size following antibiotic treatment. One patient refused operation and in the other one an elective exploratory laparotomy was done, in the course of which

no free pus was encountered. In 4 cases treated by Rutenburg, Schweinburg and Fine,<sup>134</sup> there was no apparent improvement until the abscess was drained.

When appendicitis occurs in small children, it is apt to invade the peritoneal cavity, since the thin wall of the appendix offers little hindrance to its spread, and the underdeveloped omentum fails to localize the infection. Appendiceal perforation is responsible for above 90 per cent of appendicitis mortality in children.

Joslin and Drake<sup>78</sup> have obtained good results in such cases, using oral aureomycin in the immediate postoperative period. They usually employ Wangensteen suction until peristalsis has been established, aureomycin being given through the tube, and suction stopped for 1 hour. In 16 cases of appendiceal perforation (ages ranging from 17 months to 12 years) which were so treated, there were no fatalities, and in 12 cases favorable response followed within 24 to 48 hours. Four children with appendiceal abscess showed a more gradual response, the temperature falling by lysis. No immediate surgery was done in these 4 cases, in view of the gravity of the illness, but 3 months later the appendix was removed. The results of aureomycin therapy were most gratifying, particularly in 5 children under 4 years of age.

In pregnancy, too, the danger attending perforation of an inflamed appendix is great, because of the crowding of the intestinal tract and the failure of the omentum to surround the cecum. Jones and Beatty<sup>77</sup> report the case of a young woman, pregnant 6½ months, who underwent removal of a ruptured gangrenous appendix. During a stormy postoperative course, an abscess developed in the right lower quadrant, as well as a right-sided hydrothorax, and probably an early subphrenic abscess. Response to antibiotic treatment was poor until aureomycin was begun, when the temperature dropped from 104° to normal in 5 days. Four weeks later, the patient was delivered of a normal living child. The finding, following delivery, of a mass on either side of the lower abdomen led to resumption of aureomycin therapy. Five



days later, an abscess drained spontaneously into the rectum. Both abdominal masses were drained, with rapid healing of the one on the left side. Removal of the right tube and ovary, which were severely involved, was necessary before the swelling on the right side completely disappeared. Rapid recovery followed, and the patient once more became pregnant.

Sinha<sup>154</sup> has reported the disappearance of an appendiceal abscess under treatment with oral aureomycin. The patient was referred to the hospital after being treated for "dysentery" for 12 days, without relief. Clinical recovery was complete in 6 days, and interim appendectomy was recommended.

*Dental*—Aureomycin has been found of benefit in the prevention, abortion and control of dental abscess.<sup>76,166</sup>

Selib and Selib<sup>146</sup> used combined oral and local aureomycin therapy, or topical aureomycin alone, in 6 cases of pyorrhea, with pericemental and pericoronal involvement and purulent pocket formation, in conjunction with routine procedures. In all cases, aureomycin arrested the acute manifestations, improved tissue tone, and limited the progress of the infection.

Stewart and Roth<sup>161</sup> applied aureomycin cones subgingivally in 5 cases of chronic suppurative pericementitis and 13 cases of isolated periodontal pocket, and placed the cones within the incised abscess area in 2 cases of periodontal abscess. In all cases, there was relief of pain and reduction of infection. Similar good results were obtained with aureomycin troches in 2 cases of chronic suppurative pericementitis.

Rovelstad and Castaldi<sup>129</sup> have found aureomycin to be far superior to local applications of heat or to penicillin, in the treatment of acute alveolar abscess in children. Of 16 cases treated by hot applications and symptomatic therapy, 10 required drainage or ruptured spontaneously (63 per cent). Of 27 cases given sulfonamides orally, 14 required drainage or drained spontaneously (51 per cent). When penicillin was used, 7 of 22 cases (31 per cent) either required drainage or drained spontaneously. In 28 cases

treated with oral aureomycin alone, there was no need for incision or drainage, or for opening through the tooth, and none of the abscesses ruptured and drained. There was little difference in the duration of acute symptoms in the first 2 groups, but definite improvement in this respect when an antibiotic was given. The difference was even more apparent when the length of time required for all symptoms to subside was taken into consideration; when heat alone was used, nearly 7 days; with sulfonamides, about 6½; with penicillin, less than 6 days; and with aureomycin, less than 2 days. Infection was thus checked and localized by aureomycin before pus could accumulate.

*Liver*—Chandler, Schoenbach and Bryer<sup>25</sup> have reported the case of an infant, admitted with eczema and hypoproteinemia, who developed hemolytic staphylococcal septicemia with peritonitis and multiple liver abscesses, despite high doses of penicillin, streptomycin and sulfonamides. Negative blood cultures were obtained within 5 days after starting aureomycin, and recovery was rapid and uneventful. Secondarily-infected amebic liver abscesses can be treated satisfactorily with aureomycin, as noted in the section on amebiasis. A case of recurrent cholangitis with probable abscess, due to *B. funduliformis*, is described in the section on biliary disease. Rutenburg and co-workers<sup>134</sup> reported 2 cases of liver abscess successfully treated with aureomycin. From one, a subhepatic abscess associated with gangrene of the gallbladder, hemolytic *Staph. albus* was cultured; the other, a case of suppurative hepatitis following operation on the biliary tract, yielded *E. coli*, *B. proteus vulgaris* and Gram-positive cocci.

*Parotid*—Lewis<sup>90</sup> has presented a case of acute suppurative parotitis, with blood culture positive for *Staphylococcus albus* and a hemolytic streptococcus, in an eleven-day-old child. Combined treatment with parenteral penicillin and oral aureomycin was followed by uninterrupted recovery. Multiple skin pustules, which had developed while penicillin was being given, cleared up when aureomycin was added. The mother had a secondary mastitis, which

was treated with penicillin. Cathala and co-workers<sup>21</sup> reported the case of an infant of 1½ months, with persistent fever and weight loss, several days after incision of a parotid abscess. There was marked dehydration and weakness and copious diarrhea. Improvement commenced the day after beginning aureomycin and subsequent recovery was smooth.

Puig and Bertrand<sup>117</sup> have given aureomycin to a patient with parotitis, occurring during the course of brucellosis. The patient was afebrile in 4 days and has been in good health since.

Acute purulent parotitis, developing in an elderly man after intestinal resection, while he was receiving penicillin and streptomycin, is reported by Rutenburg and associates.<sup>134</sup> The patient's condition had seriously deteriorated, when aureomycin was substituted for the previous medication. Within 96 hours, all signs of parotid infection had disappeared.

## *Amebiasis*

No one therapeutic agent has been completely satisfactory in the treatment of amebiasis. The older oxyquinoline derivatives and arsenicals were relatively effective in clearing the intestinal tract of both trophozoites and cysts of *Endamoeba histolytica*, but they possessed considerable toxicity, and relapses tended to occur. Emetine, although useful in systemic amebiasis, is ineffective against the cysts, and additional drugs have always had to be used for clearing the intestinal tract. The need has long been apparent for an amebicide which would be effective for both trophozoites and cysts; which could be used for both intra- and extra-intestinal amebiasis; and which would be nontoxic, so that it could be employed safely in ambulatory patients.

Clinically, aureomycin compares favorably with the standard remedies, without having their systemic toxicity.<sup>63</sup>

Aureomycin is active against *E. histolytica*, in both cystic and trophozoite forms, and may have an actual amebicidal action.<sup>73</sup>

Biegeleisen and Shaffer<sup>16,148</sup> have found that aureomycin inhibits the growth and multiplication of *E. histolytica*, at concentrations of 0.029 to 0.059 mg. per cc. of medium, and have presented evidence suggesting that at higher concentrations it may also be amebicidal. All 3 strains of *E. histolytica* were completely inhibited with a concentration of 0.059 mg. of aureomycin per cc., and there was marked inhibition in 2 strains and complete inhibition of 1 strain in 48 hours at a concentration of 0.029 mg. per cc. There were indications that at these concentrations actual destruction of trophozoites took place. No evidence of cyst formation was seen.

Hall<sup>60</sup> states that 25 micrograms per cc. of aureomycin inhibited the motility of the trophozoites in 4 hours, while with 100 micrograms per cc., most of them stopped moving in three-quarters of an hour. Lysis of the trophozoites was observed in concentrations of 500 to 5,000 micrograms of aureomycin per cc. In the absence of aureomycin, the trophozoites remained actively motile for at least 24 hours.

A pitfall in the differential diagnosis of dysentery has been pointed out by Jung and Beaver.<sup>79</sup> Combined infection with whipworm and ameba may be attributed solely to amebiasis. The amebic infection may be cured with aureomycin, but unless hexylresorcinol is given for the helminthic infestation, symptoms will persist.

According to Radke,<sup>120</sup> certain features are common to most cases of amebiasis. Onset is typically with an explosive diarrhea, often containing blood. This is followed by a period of intermittent cramps and diarrhea, and by extreme fecal urgency, the so-called "precipitate stool." This is not diarrhea, but actually a soft stool, and its passage may be followed by constipation for several days. Examination of the "precipitate stool" indicates that it represents a clearing of the entire bowel from stomach to rectum, so that the subsequent constipation is merely failure of the bowel to provide material for a movement. Flatulence is very

common. It is almost invariably observed that, in children, behavior becomes a problem. Radke has employed aureomycin with dramatic relief of symptoms within the first 2 days.

At least 10 per cent of the population of the United States is infected with *Endamoeba histolytica*. In advanced cases coming to autopsy, the incidence of hepatic involvement ranges from 7.6 to 84.4 per cent with an average of 26.6 per cent. In the experience of DeBakey and Ochsner,<sup>36</sup> the incidence of hepatic involvement among all cases of intestinal amebiasis during a 20-year period was 11.1 per cent. Pathological examination indicates that the usual route of entry into the liver is through the portal system; direct extension through the bowel wall or transportation by the lymphatics is rare, if it does occur.

In the early phase of amebic hepatitis, there is a balance between healing and progression toward suppuration. This balance may be upset by a number of factors, including the presence of pathogenic bacteria and perhaps of other detrimental agents such as alcohol or trauma. The signs and symptoms of amebic hepatitis may develop in patients who have never had dysentery. The authors found that about a third to a half of the patients gave no history of diarrhea. Characteristically, pain and tenderness are observed in the right upper quadrant of the abdomen and hepatomegaly is present in well over three-quarters of the patients. There may be involvement of the pleura and lung adjacent to the liver. X-ray examinations are of value in the differential diagnosis of amebic infections of the liver and its surroundings.

Multiple abscess formation gives an extremely serious prognosis. All of such patients observed by DeBakey and Ochsner<sup>36</sup> died. The fatality rate was only 11 per cent among patients with a single abscess. Most amebic hepatic abscesses are fortunately sterile, but secondary infection rapidly changes the prognosis for the worse.

Thiodet and co-workers<sup>167</sup> found that in a case of suppurative amebic hepatitis, with rupture into the bronchi, emetine had no

effect upon the abundant expectoration, relieving only the pain. Aureomycin, on the contrary, had a spectacular curative action. In another case, that of an amebic hepatic abscess which had not ruptured, aureomycin had comparatively little effect, while emetine associated with aspiration produced rapid cure.

DeBakey and Ochsner<sup>36</sup> noted impressive response to aureomycin in 1 case of hepatic abscess, which was aspirated. Within a few days after the institution of therapy, the clinical manifestations subsided, the temperature returned to normal, and the amebae disappeared from the stools. No evidence of recurrence was observed during a 4-months' follow-up.

Stapler<sup>158</sup> reports that in 24 per cent of 100 cases of amebic colitis with negative stool examinations, rectal scrapings were positive for the ameba, and stresses the value of this examination as an important means of diagnosis, and as an aid to evaluating treatment. The importance of tenderness to palpation in the left hypogastric area is indicated by DaSilva Mello,<sup>34</sup> as a sign of latent asymptomatic amebic infection of the liver. A history of such manifestation is also important.

Hall<sup>66</sup> has reported the results of aureomycin treatment in 20 cases of amebiasis, mostly in veterans of World War II. Nineteen of the cases were chronic ones; 1 (the only fatal case) had acute fulminating disease. There were 10 patients with chronic amebic dysentery, 6 carriers (passing cysts) and 4 with infection of the liver. The dysentery cases were of 4 to 8 years' standing, and 4 had received prior treatment with various amebicides. Complications included rectal ulcers in 4 cases; distortion of the large bowel and cecum in 5; regional ileitis in 1; hookworm infestation in 1; and acute brucellosis (abortus) in 1.

After a treatment course of 0.5 Gm. of aureomycin every 6 hours for 10 days, 7 of the 10 patients with dysentery remained free of either cysts or trophozoites in the stools during at least 12 to 14 months follow-up. One patient became an asymptomatic carrier, 1 suffered a relapse; but this relapse may only have been

apparent, since it was not clear that the trophozoites in the feces were pathogenic and *E. gingivalis* was present in the mouth. Temporary improvement occurred in the third patient, who, however, relapsed shortly after treatment. The amebae once more disappeared after a second course. In most patients, symptomatic improvement was prompt and usually lasting. Corresponding improvement in objective findings was observed, blood disappearing from the feces and mucosal ulcerations healing. Cysts disappeared from the stools of all of the cyst-passers, and no parasites were found in any of their stools within 6 months after treatment.

The results of aureomycin treatment in cases of hepatic involvement were less satisfactory. Of the 3 patients with hepatitis, only 1 appeared to be cured, and 1 patient with liver abscess had no subjective relief from aureomycin; amebae, however, disappeared from the stool. The 2 other patients with amebic hepatitis, not responding to several courses of aureomycin, recovered after treatment with a combination of emetine hydrochloride and diiodohydroxyquinoline. All the amebic cyst-passers were apparently cured.

As yet, no remedy has been found which will insure against recurrence of the parasites. However, even when amebae reappear in the stools after treatment, the recurrence is often asymptomatic and may indicate reinfection.<sup>99</sup> The economic and social background of the patient must be taken into account when considering the end results of therapy.

Hargreaves<sup>67</sup> states that, in 12 cases of amebic dysentery treated with aureomycin, rapid response occurred; but 2 had cysts in the stools a month later and 1 suffered a complete relapse after 6 weeks. Another patient developed amebic hepatitis 3 months after treatment. Hargreaves agrees with other workers<sup>6,115,168</sup> that, in view of the relatively high relapse rate known to follow antibiotic therapy in amebiasis, some other amebicide, like diodoquin or emetine, should be given as well.

Brown and co-workers<sup>22</sup> state that aureomycin was successfully

used in 4 patients with amebic colitis and in 3 asymptomatic cyst-passers. No relapse was observed in any patient who had been given 3 Gm. of aureomycin daily for 10 days. There is still some uncertainty as to the best regimen for antibiotic administration, in diseases with a marked tendency to relapse. Higher dosage and prolonged maintenance therapy have been advocated.<sup>14,65,74,162</sup> Short intensive courses, with brief intervals, may permit the host to build up and reinforce immunity to the parasite.

Gilchrist<sup>64</sup> states that, as a result of his experiences as a medical missionary in Portuguese West Africa, he feels aureomycin to be the most valuable weapon now available for the treatment of amebiasis, particularly under such primitive conditions as he encounters. During 1951, 25 cases of amebic dysentery with positive stools were treated, at least half of them being severe cases. Every patient showed relief of symptoms in 24 hours, and clinical cure was obtained in 3 days at the most, in all cases. It was not possible to make follow-up stool examinations for parasites.

Calero<sup>23</sup> has reported the results of aureomycin treatment in 44 patients ranging from less than 10 to 60 years of age. Forty-two of the patients were treated as clinic or office patients, the 2 who were hospitalized having liver involvement. These patients form an unselected series, representing consecutive cases diagnosed as amebiasis. The dosage was about 30 mg. per kilo per day, and the total dose ranged from 3 to 15 Gm., depending on the body weight. All stools were negative at the end of treatment and for 4 weeks later. At the end of 6 months, 38 patients still had negative stools. Calero observes that the effectiveness of a short course of therapy on an outpatient basis; the low toxicity of the drug; and the 86 per cent cure rate, indicate that aureomycin administered alone is perhaps the most effective known treatment of amebic dysentery.

Ley and co-workers<sup>91</sup> gave aureomycin to 16 persons with stool cultures positive for *E. histolytica*, but with few or no symptoms. In all cases the feces became clear of the parasite in the first 6 days, and the patients reported that they felt better by the end of



the course of treatment. Cysts reappeared in the feces of 2 patients, 2 weeks and 6 months respectively, after treatment. Re-treatment of the 2 relapsed cases produced cure in 1, but the other patient had again relapsed when seen 6 months later. An additional 4 patients were at first treated with chloramphenicol, but when it became evident that this antibiotic had no definite effect, aureomycin was given. A number of the above patients had mixed parasitic infections. It was found that aureomycin was effective against *E. coli*, *Endolimax nana* and *Iodamoeba buetschlii*, but that *Trichuris trichiura* and hookworm were apparently resistant.

As has been noted by Armstrong and co-workers,<sup>6,7</sup> the effect of aureomycin is better on chronic amebic infections than on acute ones, and this was confirmed by Ley's<sup>91</sup> findings. In 12 patients with acute amebic dysentery treated with aureomycin, in Malaya, clinical and parasitic control was obtained regularly, but permanent cure was seen less often. In 8 patients who were examined later, the amebae reappeared within a month in 3 cases.

Halawani and co-workers<sup>65</sup> have compared the antiamebic power of various remedies. Of 32 cases treated with emetine, 14 relapsed within 40 days, a relapse rate of nearly 50 per cent. Six of 10 cases who received bismuth-oxy-para-N-glycolarsenilate (WIA) and Enterovioform suffered a relapse within 40 days. Among 25 patients receiving aureomycin (20 Gm. in 10 days), there were only 7 relapses in the same period. Armstrong<sup>6</sup> found 94 per cent successes with aureomycin, 50 per cent with emetine; absolute failures with aureomycin, 2 per cent, with emetine 28 per cent. He and his colleagues consider aureomycin to be the most successful single agent for the treatment of acute ulcerative amebiasis, approaching the ideal for the ambulatory treatment of amebic infestation.

DeVasconcelos<sup>37</sup> has treated 20 cases of amebiasis with aureomycin and obtained clinical cure in 60 per cent. Other authors<sup>6,62,104</sup> have reported cure rates of 80 or 90 per cent and higher.

Radke<sup>120</sup> feels that the most effective treatment for amebiasis

is a combination of atabrine-carbasone with aureomycin, particularly in difficult relapsing cases. One of his patients was in a serious condition with hepatic abscess and involvement of the lungs and pleura, but made a complete recovery when this combined medication was used.

Saíñz<sup>136</sup> states that aureomycin should be used in preference to emetine for: small children, pregnant women, and persons with cardiorenal disease. Its immediate effect, at least, seems to be superior to that of other amebicides, and it is often effective where standard remedies have failed.<sup>6,18,62,74,101,104,152,153</sup> Since it destroys both the cysts and the trophozoite forms of *E. histolytica*, aureomycin should be an important aid in the control of the carrier state.<sup>170</sup> It seems to be of value in amebic hepatitis, and is without serious toxic effects even in the presence of liver involvement,<sup>63,84,102,167</sup> but its present accepted usage is in intestinal amebiasis.

Admitting that aureomycin does not prevent relapses of amebiasis in all cases, Fauvert<sup>48</sup> notes that neither does emetine, and points out that it is less disagreeable to take aureomycin than to undergo emetine treatment.

## *Biliary Tract Infection*

Aureomycin is peculiarly adapted to the treatment of biliary infections, because of its high degree of penetration into the normal liver and its highly concentrated excretion in the bile. The concentration of aureomycin in the bile is 8 to 16 times that found in the serum.<sup>72,163</sup> It has been used with excellent results in the preoperative and postoperative management of infection in the biliary system.<sup>3,19,55,122,175</sup>

Complete relief is rarely obtained by operation on the gall-bladder, when previous symptoms have been indefinite. The best results are obtained in patients who have had demonstrable biliary stasis arising from cholelithiasis.

Although infection is believed to play little part in the causa-

tion of gallstones, in the presence of calculi, with consequent stagnation of bile, secondary infection is apt to be a serious complication. Anderson and Priestley<sup>4</sup> made a study of the bacterial content of bile removed from the common duct at operation and found that it was frequently infected, particularly when a stone in the common duct had produced biliary stasis. Operation on the common bile duct appeared to be a more fruitful cause of secondary infection than operation on the gallbladder alone, this being true even when calculi were not found. The predominant types of organisms appeared to be the same, whether stone was present or not; no particular type of organism appeared to be of special significance in stone formation. Infection, when combined with obstruction, is of greater clinical importance than when there is free drainage of bile. Even low-grade, mild infections require treatment. The existence of residual infection appears to explain, at least in part, the postcholecystectomy syndrome. It seems obvious that a wise procedure after any operation on the biliary tract, and particularly after exploration of the common duct, is to administer antibiotics. Aureomycin has been used with gratifying results in the treatment of the postcholecystectomy syndrome.<sup>103,163</sup>

Rubin and co-workers<sup>131</sup> have presented an unusual case of recurrent cholangitis and liver abscesses due to *Bacteroides funduliformis*, in which aureomycin was successful where other antibiotics had failed. The patient had undergone at least 13 operations on the liver and biliary tract within 5 years and had been jaundiced in varying degrees for 4 years. She had been given very large amounts of penicillin, sulfonamides and streptomycin without much improvement, and on admission to the hospital was given 100,000 units of penicillin every 3 hours. Chills and fever continued. Penicillin was stopped, the patient was given 50 mg. of aureomycin every 4 hours, and within 48 hours, her temperature dropped almost to normal. Treatment was continued for 1 week with considerable improvement but was halted on account of low supplies of aureomycin. Within 24 hours, the temperature began

to rise again. Penicillin and dihydrostreptomycin were given, with very little effect, and sulfathalidine was also ineffective. Aureomycin was re-administered for 16 days, with clinical improvement and decrease in fever. One day after its discontinuance, the temperature again rose and symptoms returned. Aureomycin was once more given and controlled the infection; but when the dosage was lowered (after 17 days) to 750 mg. daily, chills and fever recurred, as did pain and tenderness. The clinical impression was that of rupture of a small intrahepatic abscess. The patient was discharged on a maintenance dose of 1.5 Gm. of aureomycin daily, which was sufficient to maintain her in apparent good health. After nearly 4 months of aureomycin treatment, a generalized maculopapular rash developed, with swelling of various joints, and diarrhea. Benadryl relieved these symptoms, and the patient has continued to receive both Benadryl and aureomycin.

In a patient reported by Samain,<sup>137</sup> who had undergone repeated operations on the biliary tract and colon, only partial recovery had followed surgery. Three months after his latest operation, the patient suffered from a return of his attacks of angiocholitis, with jaundice becoming progressively deeper and with alarming deterioration in his general condition. Aureomycin controlled the febrile attacks and greatly improved his general health.

Anderson and Priestley<sup>4</sup> concluded that after any operation on the biliary tract, but particularly after exploration of the common bile duct, antibiotic therapy should be administered. For this purpose they consider aureomycin to be of value, but the choice of agent should, when possible, be governed by the type of bacteria present.

The close functional and anatomical relations existing between the liver and the biliary tract make it imperative that aureomycin therapy be begun early enough in infections of the biliary system to avoid involvement of the liver parenchyma, with possible permanent damage. Zaslow and co-workers<sup>182-184</sup> have found that,

in the absence of obstructive jaundice or liver damage, aureomycin is excreted by the liver and stored in the gallbladder in very high concentration. The existence of acute cholecystitis does not interfere with the entrance of aureomycin into the gallbladder, as long as the hepatic and cystic ducts are patent. Either obstructive jaundice or impaired liver function lessens the ability of the liver to excrete aureomycin, but when free drainage is re-established or liver function improved, the concentration of aureomycin rises toward normal. The authors place high value on aureomycin as an agent for the treatment of biliary tract infection.

Wright and Prigot<sup>175</sup> also consider aureomycin to be of great value in surgery of the biliary tract, and have reported its use in 3 cases of serious biliary tract infection, with recovery in all.

Pflanz<sup>114</sup> observed marked clinical improvement, following administration of aureomycin, in 6 cases of biliary tract infection; and 3 failures, of whom 2 had received only 750 mg. daily. In 1 case of empyema of the gallbladder, aureomycin brought about rapid disappearance of fever, abdominal rigidity and leukocytosis; although it was not possible to conclude that the empyema had been cured.

Rutenburg, Schweinburg and Fine<sup>134</sup> gave aureomycin postoperatively to 2 patients who had undergone removal of the gallbladder for acute cholecystitis, and the postoperative course was unexpectedly smooth. In 10 seriously ill patients with severe inflammation of the biliary tract, and marked toxicity, aureomycin caused subsidence of all constitutional and local signs, promptly and completely. One patient with recurrent cholangitis did not require operation. Eight of the 9 others had a cholecystectomy and 4 of them also had a choledochostomy. Four were given aureomycin before operation and all were given it after operation. In 6 patients, there was suppuration or gangrene of the gallbladder, with localized peritonitis. Four of these patients received aureomycin only, 4 received penicillin and aureomycin throughout, and in 2 cases aureomycin was added after penicillin alone had failed.

Saínz,<sup>136</sup> who has studied the effects of aureomycin on the digestive passages, has treated 4 cases of acute cholecystitis, with abdominal defense, pain in the right hypochondrium, chills and fever. Remarkable clinical improvement followed the administration of 2 Gm. daily of aureomycin. He has successfully used aureomycin in various cases of chronic cholecystitis and calculous cholecystitis. All of the patients suffered from digestive disturbances, and intolerance to fats, milk, eggs, and chocolate. In every case, there was discomfort in the right hypochondrium, with or without radiation to the scapula; and all had positive X-ray findings, confirmed by duodenal aspiration. There were altogether 32 cases, 6 with calculi and with a long history of chronic illness, sometimes for more than 15 years. In 6 of the patients, it was possible to visualize the gallbladder after aureomycin treatment, and they experienced marked clinical improvement, with disappearance of subjective symptoms. One patient had a calculous cholecystitis with empyema of the gallbladder, which produced the picture of an acute abdominal condition, and yielded to the administration of aureomycin alone; operation could then be done in safety, with extremely good results. As preparation for operation on patients of this type, Saínz recommends the following routine procedure: administration of 2 Gm. of aureomycin daily for 3 days, then lavage of the stomach and duodenal aspiration on the third day; administration of a further 2 Gm. for 2 days and repetition of the duodenal drainage. Fifteen days later, the aureomycin-duodenal drainage routine is repeated and is followed by surgical intervention. Saínz has obtained excellent results by this method, which he feels tends to clear up not only the biliary infection, but associated hepatic infection as well.

In the paper which reports these results, Saínz<sup>136</sup> mentions that he has used aureomycin in a number of vague digestive disturbances, and has been interested to observe that even when urticaria, diarrhea, and vomiting were present the drug was well tolerated; and that where other diseases such as sinusitis, gripe and mumps

have also been present, they too have responded to aureomycin.

Localized infection by *E. coli* can be successfully treated with aureomycin, particularly in cases where streptomycin is ineffective. Hauss and Veit<sup>71</sup> have seen 18 *E. coli* infections of the urinary and biliary tract respond definitely to aureomycin, in a total dosage of up to 15 Gm.

Neff<sup>106</sup> points out that in biliary infections it is usually impossible to identify the offending organism, even in a sample of the duodenal secretions, if operation is not performed; but that the wide antibacterial range of aureomycin and its effectiveness against the common invaders of the biliary system make it probable that the infection will yield to this antibiotic.

Acute free perforation of the gallbladder (without the protection of peritoneal adhesions) is one of the most serious complications of gallbladder disease. It carries a uniformly high mortality consequent on diffuse biliary peritonitis, and should be treated by immediate operation and heavy doses of antibiotics.<sup>121</sup>

Sarcoidosis is obscure in etiology, difficult of diagnosis, and empirical as to treatment. It tends to run a chronic course of about 3 to 10 years, and may end in death or chronic invalidism. Spontaneous remissions have been observed. Mast<sup>97</sup> has reported a case in which extensive involvement of the upper abdominal lymph nodes produced a picture simulating that of gallbladder disease. The case is reported here because of that resemblance. The physical and the X-ray examinations bore out this diagnosis, and operation was performed. A normal gallbladder was found, but extensive sarcoid involvement of the lymph nodes and pericholecystic adhesions were found. Following operation, X-ray examination of the lungs revealed diffuse, nodular infiltration of both lungs, characteristic of lung sarcoidosis. In view of the possibility that this disease might be of virus origin, the patient received aureomycin for a month, 2 Gm. daily for the first week, 1 Gm. daily for 3 weeks. She was also given multiple vitamins and ferrous gluconate, for secondary anemia. Her strength rapidly returned and, in 4

months, she gained 20 pounds in weight and was able to resume her profession. Six months after surgery, the lungs were almost clear and, 11 months after, physical and X-ray examinations were entirely normal; the patient felt well and had regained her previous weight. Observation was continued for 23 months from the onset of her symptoms and there was no evidence of recurrence.

## *Enteritis*

*Dysentery*—Aureomycin has made a place for itself in the treatment of infectious diarrheas, including those caused by shigellae, and in a number of instances has succeeded where standard antibacterial and dietary methods have failed.<sup>142</sup>

In 4 aureomycin-treated adult patients with *Shigella sonnei* dysentery, the temperature became normal, diarrhea ceased, and the stools became negative for shigellae within 24 hours.<sup>40</sup> Although these results are good, none of the patients was severely ill, and the course of the disease may normally terminate by spontaneous recovery. Brainerd and co-workers<sup>19</sup> have treated 2 children with shigella dysentery, with prompt response to aureomycin.

Subba Rao<sup>165</sup> has reported 2 cases of acute *Sh. dysenteriae* infection, and 2 of *Sh. flexneri* infection, in children, 1½ to 4 years old, one of whom was passing blood and mucus 30 or 40 times a day. No response had followed treatment with sulfonamides or penicillin. Remarkable improvement in the general condition, and in the number and character of the stools, was seen within 12 hours after beginning aureomycin therapy. All of the children were symptom-free in 48 hours, and the stools had become negative.

While a single course of aureomycin was found by Lieberman and Jawetz<sup>92</sup> to cure 93 per cent of 116 patients with acute shigella infection, it was effective in only 63 per cent of 78 chronic patients.

Pflanz<sup>114</sup> obtained good results in a three-year-old child with *Salmonella* (*B. enteritidis* Gärtner) enteritis, which had not responded to sulfaguanidine. Diarrhea disappeared after 24 hours of treat-



ment, although the organism was still demonstrable in the stools.

Snelling and Johnson<sup>156</sup> observed a small epidemic of acute enteritis in the Hospital for Sick Children in Toronto. There was considerable cross-infection, which eventually reached the nursery for premature babies. Elimination of the epidemic was achieved with aureomycin and, in view of this success, all of the premature babies in this unit are now placed on 50 mg. of aureomycin daily prophylactically. The authors have compared the morbidity and mortality among premature babies in the pre-aureomycin period (1947-1949) and in the aureomycin period. In both groups, any case in which death was considered to be due to congenital debility or abnormality, birth injury, or surgical condition was eliminated from consideration. This left 48 in the control series and 47 in the aureomycin series. In the pre-aureomycin group, the morbidity was 33.3 per cent and the mortality 16.6 per cent. In the aureomycin group, the morbidity was 10.6 per cent and the mortality, 2.1 per cent. The average discharge weight was higher in infants receiving aureomycin than in a control group.

Obes Polleri and Magnol<sup>110</sup> have treated 10 cases of infectious diarrhea in young children with aureomycin, with good results. In association with antibiotic administration, they use intensive dietary treatment, including the use of colloid substances, particularly gum Karaya.

Fujii and co-workers<sup>53</sup> have found that aureomycin is superior to the sulfonamides, streptomycin or terramycin in cases of infantile dysentery in Japan. Three cases that did not respond to streptomycin were later controlled by aureomycin.

In 20 acute cases of mucosanguineous colitis in children, reported by Ruiz Sánchez and Ponce de Leon,<sup>132</sup> 75 to 100 mg. per kilo per day of aureomycin were given (in dilute fruit juice) for 3 to 8 days, depending on the persistence of symptoms. The organisms identified were *E. coli*, *B. fecalis alcaligenes*, *E. typhosa*, shigella, *B. proteus*, and 3 unidentified escherichiae. The antibiotic was well tolerated and cure resulted in 19 children (95 per cent), the one

failure being a case complicated by *Giardia lamblia* infestation. Three of the patients had previously been unsuccessfully treated with sulfonamides and streptomycin. In 90 per cent of the patients, the clinical picture was completely changed within 3 days. On the average, blood disappeared from the stools within 2.2 days, mucus within 3.0 days, and pain after 1.04 days; a marked decrease in the number of stools occurred within 1.4 days, the greater the original number of stools the greater being the reduction in number. Normal temperatures were reached and maintained by the end of about 48 hours. In 2 cases (10 per cent), relapse occurred, but responded promptly to a second course of aureomycin.

Charbonneau<sup>28</sup> states that the action of aureomycin seems excellent in infectious enteritis, including that produced by shigellae, and believes that aureomycin constitutes the best form of treatment in intestinal infections of the newborn. Breast feeding appears to be an effective form of prophylaxis.<sup>61</sup> According to Graham,<sup>61</sup> diarrhea in infancy should always be regarded as of infectious origin, dietetic diarrhea being relatively unimportant. Although upper respiratory infection often coexists, he believes that the primary lesion is probably in the bowel.

Infectious diarrhea is particularly fatal in premature infants. Obes Polleri<sup>109</sup> observed a mortality rate of only 13 per cent in a group of 15 cases treated with aureomycin, a result which he feels must be considered as very good, in view of the gravity of the condition and of the fact that these children had not responded to prior sulfonamide and streptomycin therapy.

Magnusson and co-workers<sup>94</sup> have reported on the aureomycin treatment of 8 infants with diarrhea attributable to *E. coli neapolitanum*. This organism has been responsible for a number of recent epidemics of infantile gastroenteritis and appears to be spread by droplet infection. It is not inhibited by streptomycin, but the effect of aureomycin was remarkable. Young infants, and particularly premature ones, are usually most severely affected. Four of the 8 infants to whom aureomycin was given, had been admitted

to the hospital on the grounds of prematurity, and all of the 8 were less than a month old. Even after a few doses, there was improvement in the clinical condition and disappearance of the organism from the stools. In a few cases, the organism persisted somewhat longer in the respiratory tract.

Sacrez and co-workers<sup>135</sup> have treated infants with severe digestive upsets, by means of oral aureomycin, and feel that the results are clearly superior to those in analogous cases treated with streptomycin. They treated 56 infants with aureomycin, usually in conjunction with other methods of therapy, and obtained rapid improvement in 49 cases, 19 of which seemed to be definitely attributable to aureomycin alone. In only 2 infants was the treatment obviously ineffective.

Ileocolitis in young children is a very fatal condition, severe cases showing marked toxicity with convulsions, hyperpyrexia, rapid thready pulse, Kussmaul breathing, coldness of the extremities, vomiting and diarrhea. Pecache and Palarca<sup>112</sup> studied the effect of aureomycin in 113 children, divided into 2 groups, the first consisting of patients who were moribund or practically so, and who received aureomycin intravenously, supplemented by oral aureomycin and other drugs in certain cases. In none of the cases in either group was a pathogen cultured from the stools. Of the 33 patients in the group of gravely ill children, 26 had been artificially fed. Twenty-one cases out of 33 were saved, a percentage of 66.6 per cent. In the second group, consisting of 17 severe toxic cases, 44 moderately severe cases, and 19 mild infections, there were 52 complete recoveries (again a percentage of 66.6 per cent); 14 (17.5 per cent) were improved; 10 (12.5 per cent) were unimproved, and there were 4 deaths. The authors note that on the whole the effects of aureomycin were very good, although it was of course not uniformly curative. Previous remedial agents had given very little satisfaction.

Within the past 50 years, a form of diarrhea or dysentery has been recognized, produced by a ciliated protozoon, *Balantidium*

*coli*. Santos,<sup>138</sup> of Puerto Rico, has used aureomycin for the treatment of 6 cases, with satisfactory results in all, and recommends its use to his colleagues, in view of the exceedingly widespread incidence of the disease in that region. Similar results have been obtained in 4 cases, in Chile, by Neghme and associates.<sup>107</sup> The protozoon disappeared from the stools 2 to 4 days after the beginning of treatment.

Following an attack of dysentery, disability may persist for years. The chief causes for this lengthy invalidism are latent infection, food allergy, low gastric acidity, neurosis, and organic pathologic changes. Where the trouble results from infection, specific therapy will usually restore a patient to health, unless—as sometimes happens—there is a strong psychosomatic element.

Fierst and Werner<sup>49</sup> report that in a series of 150 veterans of World War II, 18 per cent showed pathogens in the stool. As a rule, the organism was either the original cause of infection, salmonella, or *E. histolytica*. When amebiasis was present, the condition could be cleared up by a treatment with 2 mg. of aureomycin daily for 10 days.

*B. mucosus capsulatus* has been reported as the etiological agent in diarrhea and in stomatitis in infancy. Sternberg and co-workers<sup>160</sup> have reported diarrhea in premature twins caused by this organism. In one of them, stomatitis was present, produced by this organism—the first case, so far as is known to the authors, in which this organism has produced diarrhea and stomatitis in the same patient. Sulfadiazine improved the clinical condition in both children, but did not eradicate the infection. Since persistence of latent infection carries the risk of possible reinfection or carrier state, aureomycin was given with gratifying results. The twins were discharged on the thirty-seventh day of life in good health, and with no trace of the organism in their stools.

*Ulcerative Colitis*—The clinical picture of ulcerative colitis is a product of many factors. Infectious manifestations are probably only secondary to an underlying dysfunction, but they act as a

major factor in establishing the chronicity of the lesions. Specific therapy of the disease as a whole is therefore impossible, and the physician's efforts must be directed toward maintaining the patient in as good a state of health as possible; while that of the surgeon is to put the diseased colon at rest, or remove it, if all medical methods fail. Aureomycin has been found to be a valuable aid in controlling secondary invasion, and reducing the risks attendant on surgical intervention.<sup>21</sup>

Rowe<sup>130</sup> points out the importance of allergy as a causative factor in chronic ulcerative colitis, and recommends aureomycin for the control of infection. In 1 case of seasonal allergy, apparently mainly due to pollen, he found it necessary to administer aureomycin intravenously for several days in order to control the secondary infection.

Kullman and Schmitt<sup>88</sup> observed that amebiasis is frequently associated with chronic ulcerative colitis. The well-known effectiveness of aureomycin in amebiasis should, therefore, make it the preferred drug in the treatment of the infectious complications of ulcerative colitis.

Wright, Strax and Marks<sup>179</sup> have discussed 30 cases of active ulcerative colitis treated with aureomycin, together with follow-up studies on 13 who were previously reported.<sup>95</sup> Eight (67 per cent) had remained completely well for a year or more, 2 had one recurrence each and 2 had several recurrences, controllable in all but one instance by aureomycin. Marked local and general improvement took place in the remaining 17. Improvement in bowel function was reflected in general (13 cases) by a definite improvement in the sense of well-being. In 5 cases there was sigmoidoscopic improvement, as evidenced by reduction of congestion, edema, bleeding and granularity of the mucosa. The marked amount of benefit afforded by aureomycin therapy suggests that elimination of infection may favorably react on the course of the disease itself. These authors believe aureomycin to be the best available drug for the treatment of chronic ulcerative colitis.

Hargreaves<sup>68</sup> noted that in some severe cases of ulcerative colitis, with fistulae and ischio-rectal abscesses, aureomycin had a dramatic effect and at times seemed to be life-saving. Bickel<sup>16</sup> obtained fair results in 2, and rapidly favorable results in 1, of 3 grave cases of hemorrhagic ulcerative colitis. The slightly elevated temperature immediately dropped to normal.

Nasio<sup>105</sup> believes that if patients with chronic ulcerative colitis are individualized as regards therapy, many of them can be "cured" (at least 3 years of observation). Careful study of the case will indicate the relative importance to be given to the various methods of attack: psychosomatic therapy; rapid restoration of nutrition; the use of a diet designed to minimize digestive secretion and gastrointestinal motility; a high "therapeutic" dosage of vitamins; administration of colloidal aluminum hydroxide by nasal tube; correction of the hypogonadism which is frequently associated; the use of nonabsorbable sulfonamides, and, at least in acute phases, the use of antibiotics, particularly aureomycin.

Kirsner<sup>83</sup> believes that only brief courses of antibiotics should be given in ulcerative colitis, since continued administration may lead to the development of bacterial resistance. In his laboratory, strains of bacteria have been isolated which resist antibiotics in much higher concentrations than those used therapeutically. Dearing,<sup>35</sup> in discussing Kirsner's observation, recommends that aureomycin be given for only 3 to 3½ days before surgery.

Streicher and Kniering<sup>164</sup> made a 1-year study on 50 patients with chronic ulcerative colitis, treated with oral aureomycin. During a 2-week course of aureomycin administration, each patient showed definite benefit, with relief of abdominal discomfort and cramping, and reduction in the number of stools, which became formed, odorless, and relatively free from blood. Strax, Marks and Wright<sup>162</sup> reported 8 patients treated with a low-residue bland diet and no drug therapy other than aureomycin. There was distinct improvement of bowel function in 6 patients; reduction of blood in the stool of 4; subjective improvement,

marked in 7 cases; and improvement of sigmoidoscopic appearance in 3. Of 30 cases earlier treated by them, 21 were found on repeat examination to be well, 5 to be improved and 4 still to be ill. In 2 patients the colitis was unchanged, 1 patient had carcinoma of the colon, and the fourth had brain tumor.

## *Liver Disease*

Aureomycin apparently exerts some protective action on the liver itself, preventing or delaying hepatic necrosis in rats fed a necrogenic diet.<sup>1,64</sup> Whether this action of aureomycin is the result of inhibition of the enteric flora, or of some metabolic action of the antibiotic, is not clear. In dietary liver necrosis, the absorption from the portal blood of hepatotoxin elaborated by intestinal bacteria may be a factor in the development of the hepatic lesion. Fisher and Vars<sup>52</sup> did not find that aureomycin protected the liver against chloroform poisoning or acted as a stimulus to the regeneration of liver protein.

Aureomycin has proved useful in chronic liver disease, particularly in the chronic residua of acute hepatitis.<sup>149,163</sup> It appears to be of definite value in hepatic failure (including acute hepatic coma),<sup>47,56,159</sup> and in the fulminating type of acute hepatitis.<sup>98</sup>

It is possible that the success of aureomycin in these overwhelming infections, as compared with the failure which has been reported in some less fulminant cases,<sup>150</sup> may arise from the greater susceptibility of actively multiplying organisms.

Watson<sup>171</sup> has pointed out that, since urobilinogen disappears more or less completely from the urine during the administration of aureomycin,<sup>140</sup> one must bear this in mind when evaluating the existence of liver damage, or distinguishing between obstructive and nonobstructive jaundice, in a patient on aureomycin therapy. Liver function tests, if indicated, should preferably be done before aureomycin therapy is started.

Baumgartel and Zahn<sup>10</sup> have obtained experimental indications

that aureomycin may act not only on bacteria but also on bacterial and cellular ferments, particularly in an acid medium, and this led them to an investigation of the action of aureomycin on bacterial and cellular ferments. They have shown that the probable origin of urobilinogen is from the liver and gallbladder bile, through the local action of cellular enzymes. The bacteria in the intestines form from bilirubin only stercobilinogen, and no urobilinogen. Oral administration of a nonabsorbable antibiotic (streptomycin) to patients with parenchymatous jaundice, while clearing the intestinal tract of organisms, did not hinder the urinary excretion of urobilinogen. In their investigations, the authors used radioactive  $N^{15}$  in glycocoll, which enters into the formation of the pyrrol ring in blood-pigment synthesis. They consider that the results of these experiments completely exclude the hypothesis of the origin of urobilinogen from enteric bacteria, and its rapid resorption into the blood stream.

Goldbloom, Steigmann and Popper<sup>56</sup> have made a study of the action of aureomycin in hepatic failure. They<sup>57</sup> used it in the treatment of 14 patients with severe liver disease, 12 chronic and 2 acute. Of the chronic cases, 8 had cirrhosis and 4 chronic hepatitis; the acute cases were a fulminating homologous serum jaundice and an acute infectious hepatitis. All of the chronic cases were in poor condition: 11 of them were going progressively downhill and showing hepatic failure. Treatment was begun as a rule with an oral aureomycin dosage of 2 Gm. daily, but 5 of the most critically ill patients were given 1 Gm. intravenously per day, until able to take it by mouth.

The reason for giving aureomycin to these patients was that, although they were getting intensive liver therapy, their condition was not improving and, in most cases, was becoming definitely worse. Two of the chronic cases and 1 of the acute cases were in hepatic coma, and 3 of the chronic cases and 1 of the acute cases were in semicoma. In chronically ill patients, aureomycin was continued for 30 to 60 days, even when improvement had set in.



The results of treatment were as follows: 8 were definitely improved, 2 slightly improved, 4 died. In the patients responding to therapy, improvement in the sensorium was the first manifestation, sometimes appearing within 24 hours. As consciousness returned, appetite improved and nausea, vomiting and abdominal pain disappeared. There was lessening of jaundice, ascites, hepatomegaly and splenomegaly, although the latter 2 signs usually decreased only after weeks of treatment. Except in 1 case, the results of laboratory tests agreed with the clinical picture. Pruritus, present in 3 cases, disappeared during aureomycin administration. The authors point out that in acute infectious hepatitis, which generally runs a mild course, the effect of aureomycin would be difficult to evaluate, but that results such as those reported here are more significant. Recovery, although only temporary in 2 instances, took place in a high percentage of their cases which, ordinarily, would have been expected to end fatally. The beneficial effects of aureomycin given intravenously suggest that its action took place in the liver itself and was not linked closely with its effect on intestinal microorganisms.

In 9 cases of hepatitis, 4 with jaundice, Saínz<sup>136</sup> gave aureomycin. Seven of the patients were unable to tolerate the drug; in the eighth case, the hepatitis was somewhat benefited, but in the ninth case, the results were brilliant, serial biopsy showing complete restoration of normal hepatic structure: clinical signs and symptoms disappeared, and there was no indication of intolerance.

Rutenburg and co-workers<sup>134</sup> report the cure with aureomycin of 1 patient with acute toxic hepatitis and 1 with suppurative hepatitis. In both there was remarkable response to therapy. In the case of suppurative hepatitis, appetite steadily improved, jaundice disappeared, the bile became sterile, and the patient recovered. In the patient with acute hepatitis, fever disappeared within 48 hours, together with gastrointestinal signs and symptoms. Aureomycin was given only for 5 days, because it was in short supply, and malaise, nausea and abdominal pain promptly recurred. After 2

days, aureomycin therapy was resumed for 9 additional days; improvement was steady from then on and the patient was well 4 weeks later.

Lentini<sup>89</sup> reported good results in 2 acute cases of epidemic hepatitis, with a drop in temperature beginning on the first day of aureomycin administration, and with rapid disappearance of all symptoms. On the other hand, some workers<sup>80,150</sup> have been unable to observe any significant effect produced by aureomycin in acute viral hepatitis with jaundice.

A bar to the adequate treatment of acute hepatitis is the fact that the majority of patients enter the hospital with icterus and often have varying degrees of irreversible liver damage. Rissel<sup>124</sup> observed that, in patients jaundiced for 2 weeks or more, no significant response to aureomycin took place. Conversely, very definite benefit followed its use in all patients treated earlier in the course of their disease. He compared 10 treated patients with 35 controls, and found that in the former group, the longest illness lasted 20 days, the shortest 10 days, the average being 14 days, while the corresponding figures in the control series were 70, 30 and 61.

Some patients have prolonged jaundice and eventually irreversible liver damage, following an attack of infectious hepatitis. One such case with jaundice of 4 years' duration was given a total of 184.1 Gm. of aureomycin in 5 months.<sup>133</sup> Subjective improvement was evident in 2 weeks. Functional tests improved during the next few weeks and icterus diminished. The patient gained 15 lbs. in weight, not due to edema. Biopsy still showed fibrosis, but less superimposed acute change.

The usual epidemic of infectious hepatitis in Egypt consists of mild cases with a good prognosis; but, in 1951, there was an epidemic in which the clinical picture was severe and in which many patients passed on to acute necrosis of the liver, with death in cholemia. Rizkalla,<sup>125</sup> reporting this epidemic, notes that cerebral involvement was a marked feature, and that the prognosis

became serious if mental and nervous manifestations were pronounced. None of the usual therapeutic agents was of any value, including intravenous glucose and the subcutaneous administration of vitamins, choline, calcium, liver extract, penicillin and streptomycin. In 2 cases with signs of cholemia, which would ordinarily be expected to have ended fatally, aureomycin hydrochloride was given and both cases recovered completely. One patient delivered a baby prematurely during her illness and grew rapidly worse after delivery, until she failed to respond to questions or painful stimuli, and could not swallow. She was believed to be suffering from acute necrosis of the liver. When she had been in coma for 7 days, aureomycin was started by nasal catheter. Marked improvement was evident on the next day, after 6 capsules had been given, and the patient became conscious and able to swallow. Rapid steady improvement followed and she was discharged completely well in 6 weeks. The infective nature of this case was proved by the accidental transmission of the disease to the attending doctor.

Another woman, who had not been expected to recover, was considered out of danger after 10 days of aureomycin therapy. A third case was that of a fifty-eight-year-old man, who had repeated attacks of fever and jaundice and was considered to be suffering from subacute hepatic necrosis. He improved on standard therapy; but after 2 or 3 weeks, the attacks recurred. Aureomycin was given for 8 days, with improvement in his general condition. At the time of the report, he had been without recurrence for 10 weeks. It is noteworthy that a physician giving intravenous glucose to the first patient pricked himself accidentally and, 18 days afterwards, developed a severe attack of jaundice. When aureomycin became available a few days later, he received this antibiotic, and made a satisfactory recovery. Rizkalla suggests that at least some cases of toxemia of pregnancy may be of infectious origin, and believes that, although as a rule, infectious hepatitis progresses favorably with supportive therapy, aureomycin should be of great

value in cases which show signs of serious liver damage.

The mortality rate in traumatic rupture of the liver is shockingly high. Prompt recognition of the condition is vitally important, although the diagnosis is usually difficult; and early surgical repair is essential. The existence of a penetrating wound in the hepatic region will suggest the diagnosis, but even in its absence the following findings are consistently present: a history of recent external injury, abdominal pain and distention, local tenderness and muscle spasm, nausea, shock, progressive drop in the erythrocyte count, and increasing white cell count. These indicate serious internal injury and internal hemorrhage. Laceration of the liver is a surgical emergency, and the greater the preoperative delay, the greater the probability of bile peritonitis. Sawyer and co-workers<sup>139</sup> feel that drainage is also necessary. The typing and administration of blood preoperatively are important, and transfusion should be continued for several days after operation. The presence of shock and of liver damage increases the demand for oxygen, so that administration of oxygen is obviously required. These authors, in view of the invariable presence of bacterial contamination, use massive dosage of antibiotic and chemotherapeutic agents, including a combination of 2 million units of penicillin, 4 to 6 Gm. of sulfadiazine, and from 600 to 1,000 mg. of aureomycin daily. Intensive vitamin therapy, parenteral and oral, is also given. They report 4 cases, all in children between 11 and 16 years of age, who were treated in this manner and recovered.

Infarction of the liver is rare, although less so than is usually thought, and carries a death rate of 50 per cent or more. It is most common in patients who have had operations for disease of the gastrointestinal tract and spleen, and may follow the ligation of one of the larger branches of the hepatic artery; or it may occur in certain medical cases, usually cardiovascular. Massive infarct of the liver is capable of producing the hepatorenal syndrome. It is possible that occlusion of the hepatic artery is not the sole cause of hepatic infarction, but that sufficient anoxemia to produce infarc-

tion may result from occlusion of the portal vein in the presence of predisposing local or systemic factors. Gas formation, seen in some cases in the infarcted area, suggests that the lesion may result from a combination of ischemia and infection. Woolling and associates<sup>173</sup> suggest that the use of large doses of penicillin and aureomycin where massive infarction is suspected may be a valuable measure.

Edgecombe and Gardner<sup>12</sup> report recovery in a case of accidental ligation of the hepatic artery. The use of measures to prevent shock, and of massive therapy with penicillin and intravenous (later, oral) aureomycin, carried the patient safely through. There was a brief episode of atelectasis, and the wound reopened after removal of the stitches on the eighth day. However, he progressed steadily to recovery, and at no time became jaundiced. Liver function tests showed normal function about 2 months after the accident.

## *Oral Infection*

Aureomycin when given systemically appears promptly in the saliva. Kraus<sup>87</sup> found that when one 15 mg. troche of aureomycin was dissolved in the mouth, the average concentration dropped rapidly in the first half hour, but was still, after 3 hours, almost 100 times as great as the highest average concentration resulting from systemic administration. Both routes, however, were effective in reducing the bacterial flora of the mouth. Topical aureomycin reaches its peak of antibacterial activity several hours after the troche has dissolved. The bacterial flora begin to return in about 8 hours and show a normal pattern after another 24 hours.<sup>86</sup>

Aureomycin has been found curative in a large variety of acute and chronic oral infections, whether of bacterial or of viral origin. Among these are: subperiosteal abscess, herpetic stomatitis and gingivitis, suppurative or necrotizing gingivitis, submaxillary adenitis, cellulitis, alveolar abscess, osteitis, diffuse osteomyelitis of the mandible, acute circumscribed osteomyelitis, periodontal ab-

cess, subacute infected lymph node, acute pericoronal abscess, subacute pericoronitis and periadenitis mucosa necrotica recurrens.<sup>8, 20, 27, 32, 38, 39, 51, 58, 59, 76, 126, 147, 151, 161, 166, 169</sup> For complete cure of the infection, dental or surgical intervention is often needed.

Roth<sup>127</sup> has observed that, following the topical administration of aureomycin for mouth infections, such as pyorrhea or Vincent's infection, or after tooth extraction, offensive odors present in the mouth are effectively and rapidly eliminated. He and Hardy<sup>128</sup> have also reported the beneficial effect of aureomycin, when used for the healing of oral infections, upon associated systemic conditions, such as bursitis, sinusitis (acute and chronic), febrile catarrh, laryngitis, pharyngitis, and tonsillitis.

Kemler<sup>81</sup> states that the lymphoid tissues of the tongue may serve as a focus of infection, even when the tongue appears normal or at most slightly coated. In many patients with unpleasant breath (*fetor ex lingua*), washing of the tongue will elicit an odor of putrefaction. When the tongue is cleaned and aureomycin given internally, not only does the breath become sweet, but secondary infections as, for example, iritis, optic neuritis, dacryocystitis and Menière's disease, also clear up. DaSilva Mello<sup>33</sup> has reported the clearing up of bad breath following the local use of aureomycin.

Having satisfied themselves of the excellent results following the use of oral aureomycin for the systemic treatment of acute necrotizing ulcerative gingivitis, Goldman and Bloom<sup>59</sup> tried its value as a topical application. In 30 patients treated by this method, results were comparable to those obtained by oral aureomycin. They consider that the success of this treatment and the absence of any undesirable reaction makes it a valuable aid in the treatment of this condition.

Frequently, mouth infections, especially those of virus origin, tend to annoying recurrences. In many cases, aureomycin appears to have cured such conditions. Sigel<sup>151</sup> has reported dramatically prompt cure, by means of mouthwashes and gargles of a 0.5%

aqueous suspension of aureomycin, in 1 chronic case of periadenitis mucosa necrotica recurrens. This disease, presumed to be of viral origin is characterized by painful recurring ulcers of the mouth and pharynx. One ulcer in the pharynx, apparently inaccessible to the gargle, responded to applications of aureomycin paste.

Gottlieb<sup>60</sup> used aureomycin locally, with marked success, in the treatment of 14 longstanding cases of recurrent oral aphthae, who had not been free from symptoms for more than 2 or 3 weeks at a time, and who were observed for 6 to 18 months after treatment. He used the antibiotic in 0.25 solution, about 8 times daily, feeling that, although troches provide an easier method of treatment, the mouthwash produced a more rapid effect with less tendency to cause mucosal irritation.

Yabuki and associates<sup>180</sup> thought that a higher concentration of aureomycin (0.5 to 1.0%) acted more effectively in 4 cases of stomatitis aphthosa, and 1 of stomatitis ulcerosa, treated by them.

## *Pancreatitis*

When 10 cc. of bile is injected into the pancreatic duct, it produces a fatal acute hemorrhagic pancreatitis in dogs; but when aureomycin is given orally for several days before or after injection, no deaths occur. Intravenous aureomycin protects only 40 per cent of the dogs. In untreated animals there is a rapid increase in the bacterial content of the liver and pancreas, consisting largely of clostridia, which are found also in the peritoneal fluid and in the blood of the portal vein. Polyvalent gas gangrene antitoxin, used prophylactically, gives a 60 per cent survival rate, and it is therefore evident that the clostridia are largely responsible for death.<sup>113</sup>

Pancreatic involvement in mumps has been favorably influenced by aureomycin.<sup>157</sup>

In a farmer who had been kicked in the abdomen, there developed 2 days later abdominal rigidity with fever, chills, coldness of the extremities, and a state of shock. Three years previously, he

had been diagnosed as having calculous cholecystitis. The leucocyte count was 16,500 and the preoperative diagnosis was possible perforated ulcer or suppurative cholecystitis. He was given careful preoperative preparation, but fever and leucocytosis persisted at the same intensity for 24 hours, at the end of which time the clinical picture and the laboratory findings suggested the possibility of a pancreatic lesion. Sáinz,<sup>136</sup> who has reported this case, states that aureomycin by mouth was given on the first day but was poorly tolerated and was therefore given intravenously. On the second day, there was a slight diminution of fever, and vomiting had almost disappeared, but the leucocyte count was still high. Believing this a case for combined antibiotic therapy, the physician gave streptomycin, chloramphenicol and aureomycin by mouth. All symptoms rapidly disappeared. The patient recovered completely but, since he refused operation, Sáinz was unable to report on the actual lesions present.

### *Perforated Viscus*

Perforation of a hollow viscus has always carried a high mortality from chemical irritation and massive bacterial contamination, even when surgical and supportive measures have been prompt and thorough. Of recent years, the outlook has been much improved by the use of penicillin and the sulfonamides, and even more by the use of aureomycin. Excellent results have been obtained by a number of workers,<sup>9,12,106,155,163</sup> in this extremely serious condition.

Schreiber and co-workers<sup>143</sup> used intravenous aureomycin initially in 15 cases of perforation, changing to oral administration as soon as possible. Following emergency operation, wound and pulmonary infections developed, but there were no multiple intra-abdominal abscesses and no septicemias; the peritoneal reaction was controlled within 5 days on the average; and the mortality was 6.67 per cent, or about one-tenth of what would have



been expected before the advent of chemotherapy. The series included 4 gunshot and 5 stab wounds of the abdomen, 1 requiring intestinal resection; 5 acute mechanical obstructions; and 1 accidental perforation. The only death resulted from shock and hemothorax, following multiple perforating and lacerating gunshot wounds of the chest and abdomen. The authors consider that the postoperative course of the survivors was relatively benign, and attribute the extremely low mortality rate to a combination of adequate surgery and postoperative aureomycin.

Olshaker and co-workers,<sup>111</sup> reporting gratifying results in 6 cases of peritonitis in children, secondary to the rupture of an inflamed appendix, recommended the intravenous administration of aureomycin as probably the most advantageous form of therapy until the patient is able to tolerate the drug orally.

Neff<sup>106</sup> describes the case of a nine-year-old girl with severe peritonitis following the rupture of an appendiceal abscess. Her very poor condition contraindicated surgery. On the fourteenth day of illness, she was given parenteral aureomycin and penicillin, with return of bowel function within 2 days and of normal temperatures within 6 days. Complete recovery followed and she later underwent an elective appendectomy.

In 27 cases of perforated duodenal ulcer with peritonitis, reported by Wright and Prigot,<sup>175</sup> there were 2 deaths, only 1 of which might be attributed to failure of aureomycin, that of a woman who died 40 hours postoperatively.

Severe accidental abdominothoracic injury, produced by a large sliver of wood which perforated the stomach and severely damaged the left kidney, has been reported by Bertram.<sup>13</sup> Operation consisted in removal of the foreign body, repair of the stomach lacerations, and nephrectomy. The wounds were closed, with drainage, after instillation of penicillin and streptomycin. The first 2 weeks of convalescence were uncomplicated, but on the fourteenth day, wound infection and fever developed. Administration of aureomycin rapidly cleared this up, and the patient, when re-

examined 10 weeks after the accident, was apparently perfectly well.

Yeager, Byerly and Holbrook<sup>181</sup> believe that, where surgery is for any reason contraindicated, a combination of aureomycin and penicillin should give excellent results. In patients unable to take medicine by mouth, intravenous administration ensures the rapid attainment of effective blood levels. In such cases, 500 mg. of aureomycin is given twice daily intravenously. If post-injection phlebitis occurs, it need occasion little concern, since it has been found to be transitory and without sequelae. As soon as postoperative Wangensteen suction can safely be interrupted, 25 mg. per kilo of aureomycin daily should be given by mouth. Schlicke,<sup>141</sup> reporting a series of cases of intestinal perforation without external trauma, states that he and his colleagues rely mainly on intramuscular penicillin and intravenous aureomycin, given at 6-hour intervals.

### *Peritonitis, Prevention and Treatment*

Although sulfonamides, penicillin and streptomycin, often in association, have come into almost routine use in many clinics, as adjuncts to surgery in peritonitis, Claisse<sup>28</sup> points out that too frequent failures still darken the prognosis. He considers that aureomycin rightfully holds first place in the treatment of peritonitis, for 2 reasons: first, its vast antibacterial spectrum; and second, the low resistance offered to it by most bacteria. He believes the logical method of using aureomycin, in cases of peritonitis, is initially by the intravenous route, later by duodenojejunal instillation as soon as Wangensteen aspiration can be suspended, and finally by mouth.

The usefulness of aureomycin in the prevention and treatment of peritonitis is unquestioned. Many reports testify to the concentrations of aureomycin reached in the bowel, to the reduction of fecal flora produced, and to the lowering of mortality and of complications, consequent on its use in actual or threatened peri-

Bierman and Jawetz<sup>17</sup> found that, when food intake was adequate, aureomycin was effective in suppressing the fecal flora for long periods, without producing toxicity or nutritional deficiency.

In experimentally produced peritonitis in dogs, Schweinburg, Fine and their colleagues<sup>144</sup> found that the cure rate with oral aureomycin was 80 per cent or more; with intraperitoneally administered aureomycin, 80 per cent; with intramuscular aureomycin, 70 per cent, and with intravenous aureomycin, 10 to 20 per cent. While the efficiency of the intraperitoneal route is equivalent to that of oral administration, it produces a chemical peritonitis itself, and may cause death if used for more than 48 hours. This route is therefore impracticable in human cases. The very low efficiency of intravenous aureomycin seems to the authors to be the result of some interference with the defense reaction by the drug, when given in this manner.

In experimental intestinal obstruction, Morton and co-workers<sup>103</sup> have found that aureomycin given postoperatively to dogs has resulted in the strangulated loops remaining intact in a high percentage of animals. The dogs survived longer on the average, and several showed no free intraperitoneal fluid, in contrast to dogs treated with aureomycin preoperatively and postoperatively, and to controls. They believe that this difference may be attributed to the overgrowth of aureomycin-resistant strains, as a result of prolonged exposure to the antibiotic during preoperative treatment.

McVay, Evans and Sprunt<sup>100</sup> stress the value of aureomycin in intestinal disease, and note that bacteriostatic intestinal levels of aureomycin are quickly reached and well maintained, following the oral use of aureomycin. Of the 8 most common pathogens producing peritonitis after intestinal perforation, 7 were significantly reduced in number, *Str. faecalis* being the sole exception.

Edmiston and co-workers<sup>44</sup> emphasize that the most important factor in the prevention of peritonitis following colon resection is care in preventing fecal contamination. They found experimentally

that prophylaxis with an antibiotic like aureomycin, is an effective means of combating contamination if it should occur. Knoblauch<sup>85</sup> recommends that aureomycin or streptomycin be given to all patients with serious infection of the abdominal cavity, or wherever there is danger of peritonitis. Hartl<sup>70</sup> gives aureomycin prophylactically to all candidates for bowel surgery, and considers peritonitis an unconditional indication for aureomycin.

Crile and Turnbull<sup>31</sup> reflect current opinion in considering aureomycin to be more effective than penicillin for prevention or cure of infections of the colon. Antibiotic preparation has made resection of the lower gut, with anastomosis, as safe from infection as is combined abdominoperineal resection, and this operation is supplanting the latter. Chemotherapy also permits primary closure of the posterior wound, if combined abdominoperineal resection is employed, and greatly reduces the length of convalescence.

Wright and his co-workers,<sup>178</sup> who have published a number of papers on the use of aureomycin in peritonitis,<sup>143,174,175</sup> have recently reported a series of 235 consecutive cases, in which aureomycin was used as the only antibiotic. In this series, there were 22 deaths, 7 of them attributable to antibiotic failure. A reduction of more than 50 per cent in both total and antibiotic mortality rates resulted from the use of aureomycin, as compared to the rates when penicillin and streptomycin were used. The authors consider aureomycin to be the antibiotic of choice in the treatment of peritonitis.

Rutenburg, Schweinburg and Fine<sup>134</sup> used aureomycin in the treatment of 24 patients with peritonitis arising from disease of the gastrointestinal tract. The bacteria isolated included 1 or more of the following; *E. coli*, streptococcus, staphylococcus, *B. proteus vulgaris*, clostridia, *Ps. aeruginosa*, *A. aerogenes*, *Kl. pneumoniae*, *B. alcaligenes faecalis* and *B. subtilis*. There were 3 deaths, 1 from fulminating ulcerative colitis with extensive destruction of the colon, 1 from persistent peritoneal contamination along a defective

suture line; and the third from septicemia following neglected appendicitis. The remaining 21 patients recovered, and in 13 of them the smoothness of the postoperative course appeared to be unmistakably due to aureomycin therapy. Five patients were given both penicillin and aureomycin but, while penicillin might have been of value as a supplement, it was apparently not responsible for controlling the infection, since 4 of these patients had already been receiving penicillin without evident benefit.

Of 27 patients who underwent operation for a variety of gastrointestinal lesions, and who were given aureomycin preoperatively, 23 had a smooth and rapid convalescence without complication; a remarkable finding, in that most of them were more than 60 years old, and many had chronic disease of the heart, vessels, lungs or kidneys.

To 40 additional patients subjected to major operation on the digestive tract, the majority of them already suffering from infection, aureomycin was given postoperatively. Sixteen patients received penicillin, and 2 received streptomycin and penicillin, in addition to aureomycin. No peritonitis nor urinary infection developed in any patient, although 8 of them were on continuous bladder drainage and 9 required repeated catheterization. The occasional febrile episode was mild and brief, and all wounds healed by primary intention. In this latter group, there were only 4 postoperative complications: 2 wound infections and 1 intra-peritoneal abscess, all of which responded to drainage, aureomycin and supportive therapy; and 1 thrombophlebitis of the deep leg veins with pulmonary infarction, which was treated satisfactorily with anticoagulants.

Under aureomycin protection, Crile and King<sup>30</sup> performed a very extensive operation on a sixty-two-year-old woman for a carcinoma of the transverse colon, that was invading the abdominal wall. The entire carcinomatous area was removed as a whole, followed by end-to-end anastomosis of the colon. The area of abdominal wall removed was 12 x 15 cm. and the defect was

closed by the use of tantalum mesh. In spite of the presence at operation of massive fecal contamination, healing of the wound progressed satisfactorily, convalescence was uneventful, and 6 months after operation, the patient was apparently well.

Vascular injury to the intestine, whether resulting from local disease or from the surgical measures directed towards its cure, is one of the dangers attendant on bowel surgery, and one of the important factors in producing leakage after one-stage resection and anastomosis. Rabinovici and Fine<sup>119</sup> state that, with suitable chemotherapy, even severe vascular injury will heal. They have found experimentally that aureomycin by mouth hastens the re-establishment of normal circulation in a loop of intestine subjected to either arterial or venous injury of such extent that gangrene and death would otherwise result in about 40 hours. This is not the case, however, if both venous and arterial occlusion are present.

Nikischin<sup>108</sup> concludes from his observation of 7 cases of peritonitis treated by means of aureomycin, that aureomycin is superior to the older antibiotics, that its action begins within the first 24 hours, that the subjective improvement parallels the objective improvement, that aureomycin can if necessary be used satisfactorily with other antibiotics or with the sulfonamides, and that its special value lies in its action against those microorganisms which are resistant to penicillin and streptomycin. Pulaski and Shaeffer<sup>118</sup> feel that aureomycin promises to supplant both of these latter antibiotics, whether used separately or together.

Wright and co-workers<sup>163,174</sup> believe that initial intravenous injection of aureomycin, followed as soon as possible by oral administration, is the best procedure in peritonitis. They have given 500 mg. in 500 cc. of 5% glucose twice daily by vein, then 500 mg. orally twice daily for about 7 to 10 days. A chemical phlebitis occurred in some patients but did not prolong their illness.

Their results compared so favorably with those obtained with other treatment regimes, reducing the mortality rate by 50 per

cent,<sup>163</sup> that although they had begun with a control group treated with penicillin and sulfadiazine, they decided that the use of aureomycin was indicated in all cases of acute peritonitis.

Reynolds<sup>123</sup> stated that he had seen an occasional child with peritonitis, whose infection appeared resistant to the usual doses of penicillin and streptomycin, and even to unusually large amounts, but who responded in a spectacular manner to intravenous aureomycin.

Ingelrans and co-workers<sup>75</sup> reported cure of 1 infant with appendiceal peritonitis, and Olshaker and co-workers<sup>111</sup> obtained similar results in 6 additional cases. Appendectomy was done in all cases, and drainage in 5. The results of treatment were good, except that in the one case which was not drained, elevation of temperature persisted and a wound abscess developed. The authors therefore believe that a combination of appendectomy and tight closure, with drainage, is the operation of choice. All of the children were discharged well, 6 to 18 days after admission.

## *Rectal Infection*

When suitable antibiotic preparation has been given for anorectal surgery, postoperative healing time is reduced to about one-third and the incidence of skin tags to less than one-tenth, with marked decrease in the amount of postoperative fibrosis.<sup>69</sup> Coffey and Brinig<sup>29</sup> prepare patients having large bowel polyps by the pre-operative use of oral aureomycin, a low-residue diet, and rectal irrigations.

Logan and associates<sup>93</sup> have successfully used aureomycin in 9 cases of ischiorectal abscess. Two of the patients had previously undergone surgery for hemorrhoids or for fistula-in-ano. In 1 case, incision and drainage was performed before admission; in 1 case, spontaneous rupture had occurred before institution of aureomycin therapy. In only 1 case was surgical interference needed after beginning aureomycin. In the remaining cases, pain ceased promptly

and spontaneous rupture of the abscesses occurred within a few days. All of the lesions healed cleanly and completely within 4 to 11 days.

Aureomycin is highly effective in lymphogranuloma venereum. Ahufelt<sup>2</sup> reported apparent cure of a rectal stricture caused by lymphogranuloma inguinale, using only aureomycin and dilatation by means of a bougie. Many chronic rectal cases, however, require surgery for relief of stricture. For these patients, an adequate course of aureomycin is recommended during preparation for operative intervention.<sup>116,176,177</sup>

The surgical treatment of lymphogranulomatous stricture has until recently been dangerous, since no specific agent was available for the control of infection. Eiseman and Mueller,<sup>45</sup> note that operation can now be made more extensive and much safer. They describe a new procedure to remove the diseased intestine without resort to colostomy, using a portion of the ileum to repair the defect and restore bowel continuity with the intact anal sphincter. They report 1 case so treated, following the patient's plea for closure of her colostomy. Aureomycin was used before and after operation. There were no complications, and bowel function was completely restored.

Prigot and his associates<sup>116</sup> have administered aureomycin to 4 patients with lymphogranulomatous rectal stricture. One had undergone a previous colostomy and surgery was later performed in 2 others. In all cases there was relief of pain and discharge and, in the 3 without a colostomy originally, the diameter of the stools was increased.

Benign granulomatous lesions of the rectum and sigmoid colon are occasionally encountered, which bear a close resemblance to malignant growths. The granuloma may be syphilitic, lymphogranulomatous, tuberculous, or due to parasitic infestation. Belle and co-workers<sup>11</sup> have reported 2 such cases in which the history, the presence of blood in the stools, and the gross appearance and feel of the tumors suggested neoplasm. Carcinoma was considered



a strong possibility, on account of the asthenia, weight loss and fever. Biopsy, however, showed no sign of malignancy but rather a chronic granulomatous lesion. In both cases, prompt response and ultimate cure followed aureomycin therapy. The authors urge that in all cases of granuloma in this part of the intestinal tract, in which malignant neoplasm cannot be demonstrated on pathological study, aureomycin treatment should be tried. It may save the patient a resection of the involved bowel.

Weyrauch<sup>172</sup> has reported the successful repair of 4 cases of urethrorectal fistula. Preoperatively, he used aureomycin and sulfasuxidine, and postoperatively, penicillin and dihydrostreptomycin for 4 days, then aureomycin until the removal of the urethral catheter.

In inflammation of the rectum, consequent on the radiation treatment of genitourinary cancer, Evans<sup>46</sup> emphasizes the importance of treating bowel infection, and has used short courses of aureomycin with satisfactory results. He recommends the administration of vitamin K to all patients receiving a drug to sterilize the bowel.

Andina and Alleman<sup>5</sup> caution that when a second operation on the large bowel or rectum is contemplated, as for example, second stage operation for the removal of rectal carcinoma, the sensitivity of the intestinal bacteria to the various antibiotics should be re-determined.

# CHAPTER TWO

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## INFECTIONS PRIMARILY INVOLVING THE GENITOURINARY SYSTEM

THE adequate treatment of genitourinary infections depends, perhaps more than that of any other type of infection, on thorough diagnosis and on demonstration of all of the lesions present. The need for bringing infection under control as rapidly as possible, in order to prevent extension to the entire urinary system with possible permanent damage, makes it of great importance to determine the principal organisms present, so that appropriate antibacterial agents may be used. Infection of this tract may be the result of a primary bacterial, spirochetal or viral invasion, or may be secondary to urinary stagnation, produced by organic or functional disease. The most important requirement, and indeed the fundamental principle, in the successful treatment of urinary infections is the provision of an adequate, free, urinary passageway.

Aurcomycin is considered by many to be the most valuable antibiotic for use in infections of the genitourinary system. Features which make it particularly applicable to this type of infection are its broad range of effectiveness, the high and sustained concentrations reached in the urine, the lack of development of resistant strains even when treatment must be long continued, and the enhancement of its activity by the acidity of the urine. It is particularly useful for the preoperative preparation and postoperative care of candidates for urogenital surgery, and for prophylaxis dur-

ing manipulation or instrumentation of the urinary passages, to forestall local or blood stream invasion by pathogenic organisms.

## Abscess

*Pelvic*—Hartl<sup>61</sup> gives aureomycin prophylactically for all operative procedures of any extent on the urinary tract, in view of the likelihood of infection with *E. coli*. He cites 1 case of nephrectomy during pregnancy, for an infected hydronephrosis, and 1 of a chronic empyema of a supernumerary ureter, in which infection following operation was completely controlled by means of aureomycin. He notes that chronic recurrent infections of the adnexa, such as pyosalpinx, are favorably influenced in a very short time by this antibiotic and quotes a case of severe febrile pyosalpinx with exudation into the pouch of Douglas, yielding *B. funduliformis* in pure culture, which showed little improvement after repeated aspiration and treatment with penicillin and sulfonamides, but cleared rapidly when aureomycin was given. In another patient, with a large pelvic abscess produced by the same organism, after hysterectomy for a large myoma and an accompanying infected hydrosalpinx, rapid healing of the abscess occurred following the administration of 3 Gm. of aureomycin. Return of fever 3 weeks later, due to an abscess in the parametrium, was again controlled by a second course of 5 Gm. of aureomycin.

Hartl<sup>62</sup> writes that one of the most virulent of microorganisms is *B. funduliformis* and that it is responsible for the majority of cases of tonsillogenic sepsis. The rare funduliformis septicemia of childhood usually arises from an otitis or mastoiditis. In the adult, the portal of entry is as a rule, the nasopharynx but may be elsewhere; for example, in the female genital tract. Before the days of antibiotics, blood stream infection by *B. funduliformis* was almost uniformly fatal. The infection responds fairly well to sulfonamides, better to penicillin, and outstandingly to aureomycin, which Hartl refers to as a "sovereign remedy." He mentions a case, treated by



Ernst, of an extremely stubborn bilateral pyosalpinx which yielded a pure culture of *B. funduliformis*. Strikingly rapid healing followed the administration of only 4 Gm. of aureomycin.

*Renal*—The treatment of renal carbuncle, except for the rare one which ruptures into the renal pelvis and drains spontaneously, has hitherto always lain in the domain of the surgeon. The powerful weapon provided by antibiotic therapy has made surgery unnecessary in some instances and pyogenic processes of the genitourinary tract can today often be aborted or cured by medical means alone. The diagnosis in such cases is a presumptive one, but can usually be made with a high degree of probability by careful radiologic and urinary studies, including repeated smears and cultures.

Götzen<sup>53</sup> reports 2 cases of kidney abscess successfully treated with antibiotics. One patient was given 2.5 million units of penicillin, the other received a total of 4 Gm. of aureomycin. After taking 750 mg. of aureomycin, the second patient became afebrile, and the serious clinical picture presented on admission disappeared. A day later, he was completely free of pain and was able to get out of bed. A few leukocytes and erythrocytes were still present in the urine, but it was clear of cocci. A retrograde pyclogram made 2 weeks after beginning treatment, showed restoration to normal. In both of these cases, there was an acute severe unilateral hematogenous infection, which would ordinarily have required operation. The author recommends that a brief trial of antibiotic therapy always be made in this type of renal suppuration, before having recourse to surgery.

Bruskewitz<sup>16</sup> has reported the case of a patient with bilateral polycystic kidneys and a carbuncle of the lower right calyx, successfully treated by penicillin, aureomycin and chloramphenicol. The patient was discharged, asymptomatic and with sterile urine, 6 weeks after admission and was maintained for 1 week on Gantrisin. She has remained apparently well since. The time elapsing between the beginning of treatment and her return to full employment was 37 days.

Schoenbach<sup>126</sup> has cited the case of a man of 61 with carcinoma of the bladder, who developed coli-acrogenes pyelonephritis. Bilateral ureterosigmoidostomy and bilateral nephrostomy were performed, and multiple abscesses in both kidneys were found at operation. The infection, which had been uncontrolled by penicillin and streptomycin, cleared following administration of aureomycin, and the patient was afebrile and draining into the sigmoid on discharge.

Furlong<sup>51</sup> described a case in which heminephrectomy was performed for a staghorn calculus in the lower half of a double kidney. An abscess developed in spite of streptomycin therapy and spontaneously discharged about 30 ml. of pus on the tenth postoperative day. Institution of aureomycin therapy then gave satisfactory progress.

### *Cervicitis and Vaginitis*

Good clinical results have been obtained by the use of aureomycin suppositories, in cervicitis and vaginitis due to trichomonal infestation.<sup>57</sup> *In vitro*, aureomycin and tyrothricin have much greater trichomonocidal potency than have chloramphenicol, penicillin and streptomycin, although streptomycin had previously been found to give better clinical results than any other remedy. McVay and co-workers<sup>87</sup> observed rapid subjective and objective improvement following the topical use of aureomycin in 31 nonpregnant and 12 pregnant women with symptoms, and clearing up of infection in 11 patients without symptoms, who were not pregnant. No sign of either systemic or local tissue reaction was observed, except for mild local discomfort in 9 cases. In 3 cases among the pregnant women, and 3 among the nonpregnant ones, trichomonads reappeared, but without accompanying symptoms, except in 1 member of the former group. A second aureomycin treatment usually controlled the recurrence.

In infection of the vaginal mucosa secondary to senile atrophic changes, Chatham<sup>24</sup> has found that the use of 1 capsule of aureo-

mycin intravaginally every 12 hours is apparently superior to that of sulfonamide creams.

Schwartz<sup>128</sup> has reported dramatic response to aureomycin in a severe case of ulcerative vaginitis due to *E. coli*. The condition had failed to improve on local and general treatment, including intramuscular injection of penicillin, and urination became so difficult and painful that it was necessary to admit the patient to a hospital, and catheterize her under pentothal anesthesia. Within 24 hours after beginning oral administration of aureomycin, her condition was transformed, and she was discharged cured at the end of a week.

## *Chancroid*

Rapid healing of ulcers and reduction of inguinal adenitis follow the use of aureomycin in chancroid.<sup>12,27,100,152</sup> Scott<sup>129</sup> has recorded that the hospital stay is less for patients treated for chancroid with aureomycin than for those treated with sulfonamides. He observes that because aureomycin given in sufficient quantity to cure chancroid may either mask the early signs of syphilis or lengthen its incubation period, all patients receiving aureomycin for chancroid should be followed with monthly serologic tests for lues.

Aureomycin has also been shown by Willcox<sup>141</sup> to be effective in aborting infection in volunteers inoculated with chancroid, control of the infection being tested by the intradermal injection of bubo fluid from a treated donor into a healthy volunteer. Small doses of aureomycin caused the bubo fluid to lose virulence within 24 hours.

Charpy and co-workers,<sup>23</sup> however, found aureomycin to be inactive in 1 case of inguinal adenitis caused by *H. ducreyi*.

## *Gonorrhea*

In gonorrheal urethritis, oral aureomycin is as effective as intramuscular penicillin and more easily administered. It produces very

few undesirable reactions, and its use does not result in increased resistance of the gonococci.<sup>26,29,34,111,146,147</sup>

Wright and associates<sup>147</sup> have reported 95.2 per cent cure in 63 patients treated with aureomycin. The cure rate should probably have been higher, since 1 patient classified as a failure had almost certainly been reinfected. The results are, therefore, almost identical with those in a group previously studied by these authors, with 96.3 per cent cures among 107 patients. The treatment course consisted of one 500 mg. capsule, swallowed in the physician's presence, followed in 6 hours by a second 500 mg. capsule. Within 24 hours, the thick purulent discharge stopped. Some patients continued to have a thin watery discharge for 24 hours more, but it contained no gonococci. Cure was considered to be attained when there was complete freedom from all signs and symptoms, with negative smears and cultures at 3 consecutive examinations. This result was observed in all but 3 patients, one of whom had apparently been reinfected, since a second course produced cure; the other 2 patients had taken only the first capsule, stating that they had lost the other.

The authors conclude that the dose used in this study is the minimal effective dose for gonorrhea, that higher dosage is undesirable, that aureomycin should prove equally efficacious as a prophylactic agent, and that 1 Gm. should in theory protect a person for about 48 hours.

One hundred proved cases of gonorrhea, treated by Chen, Dienst and Greenblatt,<sup>26</sup> were arbitrarily divided into 2 groups of 50 each and given aureomycin to be taken at home. Group A was given 1 Gm. 3 times daily for 2 days; Group B, 1 Gm. 3 times daily for 1 day (750 mg. per dose in the case of 1 eleven-year-old child). On re-examination 1 week later, only 1 failure was found in each group. In 10 patients, the disease had failed to respond to other forms of therapy.

The cure rate (98 per cent) obtained in both groups compares favorably with that for the single 300,000 unit dose of repository

penicillin (90 to 95 per cent) and is better than that obtained with 24 patients given the same amounts of chloramphenicol for 1 day (70 per cent) or 2 days (92.6 per cent). A total dose of 3 Gm. of aureomycin appears to be sufficient for cure. Scott<sup>129</sup> has found that when aureomycin is given for gonorrheal urethritis in a total dose not exceeding this amount, it does not interfere with serologic or dark-field tests for syphilis, and in this respect is superior to penicillin.

In 70 patients with acute gonorrhea, given only a single dose of 1.0 Gm. aureomycin, Robinson<sup>111</sup> obtained a 70 per cent cure rate. Three of the failures did not respond later to 750,000 units of procaine penicillin.

Chen, Dienst and Greenblatt<sup>30</sup> also made a study of the effectiveness of a combination of aureomycin and chloramphenicol in the treatment of gonorrhea. They divided their patients into a group (A) of 11 patients who took 1 capsule of each antibiotic (250 mg. each) after meals, and a group of 8 patients (B) who were directed to take 3 of each in 1 dose. After 1 week the patients were re-examined and the urine cultured. All 19 patients became free of symptoms, regardless of how long the disease had been in existence. One and a half grams of the 2 antibiotics combined were apparently as effective as 3 Gm. of aureomycin or 6 Gm. of chloramphenicol. The fact that 1 dose of the combination was apparently sufficient for clinical and bacteriological cure suggests that this type of treatment deserves extensive trial, since it has the advantage of enabling the doctor to supervise the patient's medication. From 1 to 5 days were required for complete disappearance of symptoms.

Robinson and Galen<sup>113</sup> have treated 168 male patients with gonorrhea, on 133 of whom later observations were made. To reduce the likelihood of reinfection, which might be classified as failure, the wives or mistresses of the patients were also treated when possible. The treatment consisted of a single dose of 0.5 to 2.0 Gm. of aureomycin. In most cases, the discharge ceased within

48 hours. Less than 50 per cent of the 13 patients given a dose of 0.5 or 0.75 Gm. of aureomycin were cured, but in those given a dose of 1.0, 1.5 or 2.0 Gm., the cure rate was about 79 per cent. Four of the "failures" admitted intercourse during the first week after treatment. It should be noted that although the authors claim little difference in the cure rate among the higher dosages, the actual percentages given are: 77 per cent cured, of 97 patients given 1 Gm.; 87 per cent cured, of 29 given 1.5 Gm., and 82 per cent cured, of 27 given 2 Gm. A larger number of cases given the 1.5 or 2.0 Gm. dosage is desirable, to indicate the true percentage of cure.

### *Granuloma Inguinale*

Oral aureomycin has been found most effective in granuloma inguinale, hitherto a notoriously recalcitrant disease.<sup>43, 54-56, 67, 77, 100, 108, 112, 138, 149</sup> Olansky and Landman<sup>100</sup> consider it the drug of choice.

Granuloma inguinale presents a difficult sociologic and, until recently, a difficult treatment problem. In many cases of granuloma inguinale, the lesions are so extensive as to produce malnutrition, anemia and poor general health, as well as rendering the patient obnoxious to those around him because of the odor of the discharge.

Streptomycin has given outstanding results, although resistant cases are not infrequently encountered; but on the basis of reports in the literature and of their own experience, Zises and Smith<sup>153</sup> consider that the results which can be obtained with aureomycin will probably be superior to those obtainable with streptomycin. With modern chemotherapy, over 90 per cent of cases can now be cured in 1 or 2 weeks.<sup>77</sup>

In a series of 17 patients treated by the above authors with oral aureomycin, a second course of treatment was required in 2 cases, and the final result in the group after a check period of 1 to 7 months was 100 per cent cure. In 14 of the patients, all or the majority of the lesions were completely healed at the time of dis-

charge from hospital, even though the disease had lasted in some cases for several years. Zises and Smith<sup>153</sup> stress the importance of supportive therapy in debilitated patients, including transfusion, protein hydrolysates, vitamin supplements and good nursing care.

Robinson and co-workers<sup>112</sup> found that oral administration of aureomycin gave better clinical results than intramuscular injection, 27 of 36 cases treated orally showing satisfactory improvement, as against 1 of 4 given intramuscular aureomycin. Pain followed the intramuscular injections.

Of 20 cases, 5 of them resistant to streptomycin, reported by Wammonck and co-workers,<sup>138</sup> a total dose of 20 to 42 Gm. of aureomycin, during 5 to 35 days, produced consistent and permanent healing of the lesions in 16, 1 patient being permanently cured after as little as 10.8 Gm. in 20.5 days. Four patients with very extensive lesions were given a total dose of 30 to 70 Gm., which was followed by 100 per cent healing. On the average, healing was complete in 10 days after the end of treatment. Donovan bodies disappeared from the deep tissues in about 11 days with doses of 1 Gm. daily, and in about 3 days with daily doses of 2 Gm.

The minimum effective dosage seems to be 20 Gm., administered over a 10-day period, the more extensive lesions requiring more prolonged therapy.

### *Lymphogranuloma Inguinale (Lymphogranuloma Venereum, Lymphopathia Venereum)*

In lymphogranuloma inguinale, aureomycin acts rapidly on the primary infection, as well as on secondary invaders, and is considered by many to be the drug of choice.<sup>5</sup> The virus disappears from the lesions after a few days of treatment.

Ulceration of the rectovaginal septum is the characteristic lesion of lymphogranuloma inguinale in the female, extending usu-

ally into the vaginal and rectal walls and frequently to the perineum. Rectal stricture is thus more common in the female than in the male; whereas involvement of the inguinal glands is more frequent in the male. The best results are obtained in the more chronic forms of this disease, marked improvement occurring in patients with proctitis or rectal stricture, with relief of pain and an increase in the diameter of the stools.<sup>55</sup> When local surgery is required, aureomycin should be used before and after operation.<sup>2, 8, 33, 45, 63, 77, 79, 82, 90, 105, 108, 114, 119, 138, 149</sup> Wamnock and co-workers<sup>138</sup> have found that patients with rectal strictures show marked improvement when daily manual dilatations accompany aureomycin treatment, and state that, by the use of this combined therapy, colostomy can nearly always be avoided.

In a case reported by Thiers,<sup>135</sup> of a girl who had undergone an emergency operation for infection of the ischiorectal fossa accompanied by severe toxemia, there was continuous postoperative discharge of pus, with recurrent formation and closure of a fistula. Neisserian and syphilitic infection could be ruled out, but the Frei test was found to be positive. Three grams of aureomycin were given in all, over a period of 7 days. Within 48 hours after beginning treatment, the affected areas were clinically improved, and 3 weeks later cure was apparently complete.

Pagès and Quenard<sup>105</sup> reported that the administration of 50 Gm. of aureomycin to 1 patient with lymphogranulomatous rectal stricture produced rapid disappearance of functional disturbances and appreciable improvement in the physical findings. After 30 Gm. had been given, the Frei test became positive only slowly, and after 50 Gm. had been given (on the twelfth day), it remained negative. In some cases of lymphogranuloma venereum, aureomycin was not found to be effective.<sup>49, 136, 137</sup>

Charpy and co-workers<sup>23</sup> found 2 cases of lymphogranuloma inguinale to be favorably influenced by aureomycin. One of these had rectal stenosis, the other had ulcerative and fistulous manifestations in a limb.



Schamberg, Carrozzino and Boger<sup>124</sup> obtained a favorable response in 22 of 24 lymphogranuloma venereum patients with early buboes. They observed no difference between the response to 7 Gm. of aureomycin given in 7 days, and that to 20 Gm. given in 10 days. However, they recommend the latter, larger dosage. Bellows<sup>7</sup> has stated that oral aureomycin is the drug of choice in the therapy of the ophthalmic manifestations of lymphogranuloma venereum.

Fletcher, Sigel and Zintel<sup>49</sup> have studied the action of aureomycin in lymphogranuloma venereum, from the following standpoints: its effectiveness when administered orally, the clinical course of the patients after treatment, and the effect of treatment on the complement-fixing antibodies in the blood serum. They treated 19 patients with a total dosage varying between 28 and 70 Gm. of aureomycin and have followed the later course of these patients for periods of up to 1 year. Four patients with early forms of the disease, such as acute inguinal adenitis and proctitis without stricture, responded in an encouraging manner, but in 14 patients with the more chronic forms of this disease, with rectal stricture, the results were less satisfactory. In 2 of 7 patients with rectal stricture, and without previous colostomy, colostomy became necessary; while the remaining 5 showed more encouraging response. Purulent discharge and rectal bleeding rapidly ceased and bowel function was greatly improved. All of these 5 patients became normally active and felt well, but the objective improvement was rather less striking. However, in only 1 case was tenderness present at the end of an average observation period of 8 months, and in 3 of the 5 a definite increase in the diameter of the lumen of the bowel was found on rectal examination. Little, if any, effect was noted in 7 patients on whom colostomy had previously been done on account of rectal stricture. In only 2 acute cases of the entire group of 19, was there a definite fall in antibody titer of the complement-fixation test following treatment. The lack of a definite fall in the remaining patients suggests to the authors that there

may be surviving virus in the more chronic infections, even after treatment, and that it may possibly be the cause of chronic progressive disease. Similar persistence of antibodies has been observed after treatment with the sulfonamides. It is possible that only actively multiplying virus is eliminated by aureomycin treatment. The authors plan to observe these patients over a further period of several years.

Miescher<sup>90</sup> has reported a case of lymphogranuloma inguinale of 10 years' duration, with infiltration of the perineal area and with fistula formation around the rectum and the vagina. There was extreme swelling of the labia majora and the clitoris, and stenosis of the anus, which rendered defecation slow and painful. No response to any previous therapy, including the sulfonamides, had been successful. The patient was given aureomycin for 24 days, 3 Gm. daily for the first 6 days, 1.5 Gm. for the next 9 days and 1 Gm. for the last 9 days. Within 3 days, the fever and pain had regressed; and, within 10 days, the fistula had closed. Two further courses of aureomycin were given to consolidate the cure, and produced even greater improvement. Infiltration and edema of the labia completely disappeared.

In 12 cases treated with aureomycin by Banov,<sup>4</sup> and followed for as long as 18 months, results were found to be good in 6 and apparently good in another 3, but with too short a period of observation for definite statement; in 2, response was fair, and in 1 there was no change.

## *Orchitis*

Spinelli and associates<sup>131</sup> reported prompt clinical response in 4 cases of mumps with complicating orchitis, and suggest further clinical trial. They stated that it is reasonable to assume that aspermatogenesis as a complication of mumps orchitis might be prevented by the exhibition of aureomycin, since this antibiotic produced rapid subsidence of edema and reduction of testicular swelling.

Schaub<sup>125</sup> has observed that the use of aureomycin in adult cases of mumps reduces the incidence of such serious complications as orchitis and pancreatitis and, if they have already developed, reduces the length and severity of their course.

Erythema multiforme as a manifestation of neonatal septicemia has been discussed by Starr and Holliday,<sup>132</sup> who noted its occurrence, with orchitis, in a sixteen-day-old infant. The infection was controlled with oral aureomycin and parenteral penicillin; the rash faded, and the testicles and scrotum gradually returned to normal.

Remarkably beneficial effects following the use of aureomycin were reported by Layani and co-workers,<sup>78</sup> in a case of severe polyalgia and hydrarthrosis, associated with urinary infection. The patient had suffered 2 attacks of orchitis, apparently nongonorrheal in origin, the first of them associated with moderate discomfort in the lumbar region. This discomfort gradually became worse until the patient was obliged to go to bed and to discontinue activity for 4 months. He finally improved sufficiently to go to work but continued to have trouble with his back. At that time, about 2½ years before he was seen by the authors, a urogram was done but appeared to be normal. About the same time, both knees began to be painful and swollen, evidencing a bilateral hydrarthrosis which receded in a few days, only to reappear 3 or 4 times a year and to leave behind it, each time, increasing disability. Examination of the prostate showed a small nucleus of residual infection. Aureomycin was given, 2 Gm. daily for 8 days, and on the fourth day remarkable relief was experienced in the lumbar region, all movements becoming easy and free. When the patient appeared for consultation at the end of treatment, he expressed himself as astonished at the transformation in his health. Movements of the back and knees could be executed freely and without pain, although for 4 months he had not been free of discomfort, even in sleep. The patient was able, after a second course of aureomycin, to return to the very hard manual labor which was his usual work and to perform it without difficulty. He even reported having been able to

dance, about a month after he had finished treatment, a thing which he had not been able to do for 4 years.

## *Prostatitis*

Herrold and Boand,<sup>66</sup> in speaking of indications for the use of aureomycin and chloramphenicol in the treatment of urinary tract infections, mentioned that their most outstanding successes had been in the group of infections which usually follow transurethral resection. Such infections often had persisted for weeks or months in spite of the use of other antibacterial agents, whereas administration of aureomycin gave excellent results with prompt control. Occasionally, a proteus infection appeared during or shortly after therapy with the antibiotic.

Nichols and Needham<sup>94</sup> obtained surprisingly good results from the use of aureomycin in the treatment of 6 severe cases of staphylococcus bacteremia which did not respond to penicillin and other therapy. In 3 patients, the bacteremia had developed after transurethral resection. Although the condition of the patients was critical and aureomycin was instituted late, cure was achieved in 4 cases.

Merritt<sup>88</sup> reported that bacterial endocarditis had occurred 8 times after transurethral resection during a 5-year period, the incidence of endocarditis being 10 per cent in cases known to have valvular heart disease at the time of prostatectomy. He concludes that it would seem logical to administer aureomycin prophylactically, before and after transurethral prostatic resection, to all patients who have valvular heart disease.

Creevy<sup>39</sup> warns against routine preoperative catheterization which may introduce infection. He avoids this procedure unless complete retention is present, and uses aureomycin prophylactically if catheterization is necessary. If renal function is moderately impaired, the patient is given aureomycin prophylactically, and catheterization as necessary, to prepare him for operation. In pa-

tients without complications, aurcomycin is begun the night before operation. In grossly infected cases and in the presence of severe renal damage, aurcomycin is given in full therapeutic dosage, fluids are forced, and an in-dwelling catheter inserted. Bladder irrigations are given to aid in controlling infection.

The stagnation of urine consequent on enlargement of the prostate, and the rather advanced age of the average patient, have made preparation for required surgery a vitally important part of treatment. Ill<sup>70</sup> states that 20 years ago he paid particular attention to this aspect of urologic surgery, and that his death rate from suprapubic prostatectomy was 5 per cent; while surgeons who neglected preoperative care reported death rates between 30 and 35 per cent. Of equal importance is careful postoperative handling. Where infection is present or feared, the modern sulfonamide and antibiotic drugs are of great help, and Ill says that aurcomycin has saved more than one of his patients.

### *Puerperal Infection*

The raw, traumatized tissues of the genital tract after delivery afford an excellent breeding ground for pathogenic bacteria. Normally the tissues of the uterine cavity are sterile, but infection may be carried to them either by the blood stream from foci elsewhere; by introduction from without, by the physician or nurse, or by contact with infected dust or air; or, very rarely, by upward extension of the bacteria in the genital tract itself, which may develop virulence and invade the tissues.

Pregnancy and labor in themselves favor the development of infection. Changes in the liver and in the kidneys, the shock of labor, and conditions such as hemorrhage, toxemia or systemic disease, tend to lower the vitality of the patient. Other predisposing conditions are prolonged labor; operative intervention; retention of pieces of placenta, membranes or blood clots; and relaxation of the uterus.

In the majority of cases of puerperal infection, the invading organism is a streptococcus, which tends to pass promptly into the blood stream without causing much local reaction, and which produces a bacteremia of variable severity. The most dangerous infections are those which follow deep cervical tears and severe bruising of the tissues during labor, or direct inoculation of the endometrium. Puerperal infection is rarely caused by a single organism, staphylococcus, gonococcus, *E. coli* and *Cl. tetani* being among the more common additional invaders. *C. diphtheriae* has also been found not infrequently. Saprophytic as well as gas-forming organisms may be present. Infection more frequently follows abortion than normal delivery at term.

An infectious process can bring harm directly to mother or infant because of specific pathologic features pertaining to the disease, or through transplacental transfer of infection, or direct transmission during the infant's passage through the birth canal. It may cause damage indirectly, through interference with availability of nutrients or oxygen, the lack of these essentials being particularly serious for the developing fetus. Consequently, the physician who is responsible for the care of a pregnant woman always attempts to bring any infectious process under control as rapidly as possible.

For the prevention of puerperal sepsis and of the infectious complications of the post-partum period, aureomycin stands pre-eminent.<sup>61</sup> Its effectiveness against the majority of the organisms above-mentioned, its ease of administration, its prolonged blood levels, and its low toxicity render it a highly satisfactory chemotherapeutic agent.

Dramatic results have attended its use in puerperal sepsis, even when bacteremia was present and when the condition had been unresponsive to large doses of other chemotherapeutic agents.<sup>10</sup> Aureomycin passes readily into the breast milk and through the placenta into the fetal circulation, where it appears in therapeutic concentrations, giving added protection to the fetus.<sup>58, 65</sup>

Long<sup>84</sup> has given it as his opinion that all women in long or difficult labor (during which the danger of infection increases sharply) should be given 0.5 Gm. of aureomycin every 6 hours during labor, and for 48 to 72 hours after delivery. Guilbeau and co-workers<sup>58</sup> have demonstrated that its use in obstetrical cases greatly lowers the incidence of complications and of fever during the puerperium. In addition, it rapidly clears up established puerperal infections, such as peritonitis, endometritis and infected abortion.

The urinary stasis occurring during pregnancy favors infection, which, if not controlled, will involve the entire urinary tract, and which may possibly be a factor in the causation of toxemia. It is known to have a definite effect on the fetal mortality rate. Aureomycin has been found to be of great value in urinary infections in the pregnant woman.

In a group of 55 women, to whom Guilbeau and co-workers<sup>58</sup> had administered aureomycin prophylactically early in labor, only 5 developed a febrile reaction during the puerperium, and 3 of these showed a temperature above 100.4° on only 1 day. The probable causes for the 5 febrile reactions were: acute breast engorgement in 2, and a transfusion reaction, a reaction to tubal ligation, and a large degenerating myoma in the 3 others. Thus no demonstrable infection occurred during the puerperium in any woman given prophylactic therapy with aureomycin. Of 109 obstetrical patients given aureomycin, post-partum uterine cultures were positive in 11.9 per cent, as compared to 75 per cent in a control series, although all the patients in the latter group had uncomplicated, normal deliveries and an afebrile puerperium. The authors used aureomycin in the treatment of 16 patients with intra-partum or post-partum uterine infections. In all, there was prompt response to aureomycin treatment. The authors consider aureomycin the ideal prophylactic agent, and a valuable weapon for the treatment of puerperal infection.

A striking instance of the value of aureomycin in obstetrical infections is that reported by Darup<sup>41</sup> in a case of gas bacillus in-

fection of the uterus following abortion, with severe spreading peritonitis. It was felt that, in spite of the patient's extremely grave and rapidly deteriorating condition, operation was imperative. She was prepared for surgery with high doses of aureomycin, 250 mg. every 3 hours orally and 200 mg. every 2 hours intravenously without interruption for 3 days, as well as with blood transfusions and other supportive agents. The patient was obviously improved the following night, and urinary secretion, which had been completely suppressed, began again, changing during the course of that night from 60 cc. of blackish red urine to 200 cc. of clearer urine. At the same time, the evidences of peritonitis decreased, so that in 3 days, the situation was no longer critical. No hematin was found in the urine after 4 days. In all cultures a massive growth of Fränkel's gas bacillus was found. Treatment was continued with high doses of penicillin. In 10 days, the patient had only slight fever and showed no signs of peritonitis. On the seventeenth day, protected by high doses of aureomycin, she underwent total hysterectomy. The operation went well and the patient was afebrile 3 days later. While the postoperative course was not entirely smooth, no complications ensued and the wound healed by primary intention.

A case of peritonitis occurring after cesarean section, reported by Wright and Prigot,<sup>148</sup> showed no improvement in 5 days of therapy with penicillin and streptomycin, but normal temperatures were reached within 24 hours when aureomycin was substituted for these antibiotics.

Schoenbach<sup>126</sup> has reported prompt and complete recovery when aureomycin was given to a patient who had *E. coli* peritonitis following rupture of the uterus during childbirth. This infection had not yielded to administration of penicillin or streptomycin, or to surgical intervention, but satisfactory recovery followed the use of aureomycin.

Hartl<sup>61</sup> considers aureomycin to be valuable in cases of perforation of the uterus, emphasizing, however, that although aureo-



mycin provides additional security against peritonitis, it does not in any way influence the indications for operative interference. He refers to a case of his own, in which curettage after abortion produced perforation in a duplex uterus. Infection set in with severe chills, high fever, and a leukocytosis of 42,000. After 2 Gm. of aureomycin, the temperature and the leukocyte count returned to normal values and clinical peritonitis was prevented.

Schoenbach<sup>126</sup> has reported complete recovery with aureomycin in a similar case, in which *E. coli* peritonitis followed uterine rupture during childbirth and had not yielded to penicillin, streptomycin or surgery.

Cabrera and co-workers<sup>17</sup> have described a serious case of klebsiella endometritis, occurring after cesarean section in the presence of sepsis, and not controlled by heavy doses of penicillin and sulfonamides. This treatment was abandoned on the seventh post-operative day, in favor of aureomycin, 2 Gm. daily. The infection was controlled within 36 hours, and there was marked general and local improvement. Aureomycin was continued for another 48 hours, to a total of 7 Gm., and the patient was up and about on the thirteenth day.

It is pertinent to note that a number of authors,<sup>9,13,20,21,80,81,85,97,98,110,117,122,123</sup> in discussing the occurrence and prevention of infections in newborn infants, have commented upon the danger of infection developing in infants after difficult deliveries, and the wisdom of employing prophylactic aureomycin in such cases.

## *Syphilis*

The treatment of syphilis can be followed through 3 distinct epochs. The first, beginning in 1493 and lasting for 456 years, was that of empirical chemotherapy, with such agents as guaiac, sarsaparilla, and somewhat later with mercury given locally, by mouth, or in the form of injections. Potassium iodide was introduced in 1835 by William Wallace for the dissolution of infiltra-

tive and gummatous lesions. In 1909, following the identification of the *Treponema pallidum* and the development of the Wassermann test for syphilis, there began the period of specific chemotherapy which lasted for 34 years, until 1939. The fundamental dependence was upon the arsenicals, of which salvarsan was the forerunner. Finally, with the introduction of penicillin, began the present era of antibiotic therapy, whose full value we are only now beginning to realize. In fact, the statement has recently been made that syphilis, if properly treated, is the most curable and least serious of chronic ailments.<sup>35</sup>

Speaking of the continuing controversy as to the identity or nonidentity of various spirochetal diseases with syphilis, Willcox<sup>143</sup> states that, while there may be some justification for considering yaws and pinta as distinct from syphilis, there are other diseases in which the likelihood is less obvious. He includes in these "bejel" of the Middle East; the now almost extinct diseases, "sibbens" (button scurvy), of Scotland, "radesyge" of Norway; "skerojevo" of the Balkans; and the extravenercal type of syphilis seen in Turkey. He has recently compared bejel with a disease discovered by him in Southern Rhodesia, the local name of which is "njovera." This is a disease which, like bejel, is primarily a disease of children, and is usually seen in the secondary stage, followed later by gummatous lesions and osteoperiostitis. Willcox believes that njovera is probably identical with bejel, and that both are possibly transitional forms of syphilis modified by climatic, racial, and sociological conditions. It is probable that these "syphiloid" conditions will prove as amenable as syphilis to treatment with antiluetic drugs.

Although penicillin appears to exert greater immobilizing effect *in vitro* on *Treponema pallidum* than does aureomycin, and is still the drug of choice in lues, aureomycin has been found effective in experimental syphilis in rabbits, both for prophylaxis and for the treatment of early infection,<sup>140</sup> and produces rapid healing of mucosal and skin lesions in man.<sup>100, 103, 142</sup>

Irgang and Alexander<sup>72</sup> remark that the use of aureomycin in

syphilis is steadily gaining favor. They gave combined oral and intramuscular aureomycin treatment to 18 cases of primary or secondary syphilis, or having a combination of lesions characteristic of both stages; intramuscular aureomycin to 24 cases, and intravenous aureomycin to 26 cases. In every case, skin lesions responded well and surface treponemata were destroyed. Intramuscular administration was more effective than intravenous administration, although healing began earlier in the latter group. Serologic results were favorable in all cases given adequate dosage by an adequate route; the authors feel that the best results are obtainable by the concurrent use of oral and intramuscular aureomycin, although this group showed the highest incidence of Herxheimer reactions. They<sup>71</sup> believe that aureomycin may also prove to be curative in fusospirillary diseases of the skin. Rodriquez and others<sup>116</sup> have confirmed the production by aureomycin of satisfactory initial decline in serologic titer and the sterilization of surface lesions. They<sup>115</sup> reported that the results of the oral aureomycin treatment of 27 patients with dark-field-positive syphilis were comparable to those obtained in patients given 2,800,000 or 3,400,000 units of penicillin intramuscularly. Sustained high blood levels of aureomycin were easily maintained, and the antibiotic could be detected in the CSF of 50 per cent of the patients during treatment. Satisfactory serologic responses were observed, and surface spirochetes disappeared in about 39 hours on the average.

Charpy and co-workers<sup>22,23</sup> agree that aureomycin clears treponemata from the syphilitic chancre, from erosive vulvar lesions and from acneiform syphilids, within 38 hours, rapid healing following. They have found that, in general, primary and secondary clinical manifestations yield to treatment even with small doses. One case of "preserologic" syphilis remained negative during 9 days of treatment with 4 Gm. daily, and for 3 months later. During these 3 months, bismuth was also given. Two cases treated only with aureomycin, and seen weekly, showed serologic response, moderate in 1, complete in the other. The former patient

had an ulcerating gumma of the soft palate which completely healed.

Definite improvement followed the use of aureomycin in 4 cases of syphilis treated by O'Leary and co-workers.<sup>102,103</sup> In 2 patients with early acute dark-field-positive syphilis, the dark-field became negative in 16 to 60 hours and the primary lesions healed in about 16 days. One of these patients with early syphilis showed some signs of vitamin deficiency during treatment, probably as a result of interference with bacterial vitamin synthesis in the intestine. The authors now routinely administer vitamin supplements to patients receiving prolonged dosage of aureomycin.

In late cutaneous syphilis, aureomycin may produce more rapid and complete healing than does penicillin.<sup>100</sup> In 2 cases of late noduloulcerative syphilis, treated by the same group,<sup>103</sup> healing of nodular and ulcerative lesions took place. A follow-up report<sup>101</sup> on these patients showed that the spinal fluid and the blood serology of the 2 early cases were completely negative 4 months after treatment, and that, in the late cases, there had been some decrease in serology, although no significant reversal.

Aureomycin readily traverses the meningeal barrier and appears in the spinal fluid after oral administration, without the presence of actual inflammation. When there is active luetic infection of the spinal fluid, aureomycin tends to return the cell count to normal about as rapidly as does penicillin, and to produce both clinical and serologic benefit.<sup>64,102,104</sup>

In 1950, Kierland and O'Leary<sup>75</sup> stated that, while only the future could decide the eventual place of aureomycin in the treatment of syphilis, early results compared favorably with those attained with penicillin, and recommended that aureomycin by mouth be given to patients with neurosyphilis who were resistant or hypersensitive to penicillin. In a more recent article,<sup>76</sup> they report results of the treatment of 9 neurosyphilitic patients, together with further data on 10 of the 12 patients discussed in their original paper. The 9 patients who were treated with aureomycin

for the first time responded well, the results of aureomycin treatment being comparable in every way to those produced by penicillin. In the 10 patients who were observed for lengthy periods, varying from 122 to 573 days (average, 409 days), the early benefits obtained from aureomycin were continued and increased. The greatest amount of clinical improvement appeared within the first 6 to 10 months after the beginning of treatment. In 9 of the cases, the cerebrospinal fluid gradually improved. Six of the 7 patients with symptomatic neurosyphilis showed varying degrees of clinical improvement; the eleventh patient evidenced continued progression of paresis. Symptoms of neurosyphilis did not develop in any patient who did not originally manifest them.

Willcox<sup>145</sup> reported dramatic healing of the lesions of early syphilis in 11 South African natives, using very small doses of aureomycin (750 to 1,500 mg.), for periods of 24 to 48 hours. Its value, he considers, should be studied with regard to its possibilities for use by Public Health departments, in areas not staffed by medical officers and without medical facilities.

Willcox<sup>142</sup> used aureomycin in the treatment of 2 patients with seronegative primary syphilis, 2 with seropositive primary syphilis and 5 with secondary syphilis. From 750 to 1,500 mg. were given orally over 24 to 48 hours. The dark-field, which had been positive in every case, was negative in 6 of the 9 after 24 hours, and in all after 48 hours. Healing of the lesions of secondary syphilis was dramatic, and was as rapid as that following penicillin therapy. Relapse apparently occurred in 1 case. In 2 additional patients with dark-field-positive subpreputial sores, healing was complete after 3 days of aureomycin administration (total dose in each, 1.75 Gm.). Willcox suggests that 250 mg. given 4 times daily for 1 week may prove to be a satisfactory curative dose.

Willcox<sup>144</sup> notes that aureomycin, being effective against all 5 of the venereal diseases, should prove an excellent prophylactic agent, and suggests large-scale trial in some country, such as Turkey, in which prostitutes are under regular medical supervision.

Kierland, Herrell and O'Leary<sup>74</sup> have summarized results of the aureomycin treatment of 7 patients, 2 with early syphilis, 2 with late syphilis and 3 with neurosyphilis. The first 4 cases were those previously noted.<sup>102,103</sup> In the primary cases, repeated clinical and serological examinations showed no evidence of relapse during 172 and 296 days, respectively, after cessation of therapy. In the late cases, there was no change in the serologic picture during the short observation period preceding the presentation of the report.

Olansky and associates<sup>99,100</sup> also found aureomycin a promising agent for the treatment of the early and late skin lesions of syphilis. Primary and secondary lesions seemed to heal as rapidly with aureomycin as with penicillin. Jarisch-Herxheimer reactions were fewer and milder with aureomycin, thus making this antibiotic valuable in late cases, particularly those with neurosyphilis or cardiovascular syphilis. Poulin<sup>107</sup> has reported the successful use of aureomycin for the treatment of ocular syphilis, when other anti-luetic therapy had failed.

Aureomycin may become an important therapeutic agent for the treatment of syphilis during pregnancy, although it will be several years before any firm recommendations as to its use can be made. Herrell and Heilman<sup>65</sup> have demonstrated that aureomycin passes in therapeutic levels into both cerebrospinal fluid and fetal circulation. Kierland and co-authors,<sup>74</sup> although recognizing that the aureomycin treatment of syphilis is still in the experimental stage, state that for certain patients it has a clear-cut advantage, and advise it for those with penicillin sensitivity. Crawford,<sup>38</sup> in reviewing medical progress in the treatment of syphilis, commented that aureomycin appears to have antispirochetal activity, and although investigation has as yet been limited in scope, encouraging results have been obtained in treatment of early syphilis, late cutaneous syphilis and neurosyphilis.

Olansky and associates<sup>99</sup> found that best results were obtained when 60 mg. of aureomycin per kg. per day were administered for

8 days. Organisms disappeared from surface lesions at a slower rate than with penicillin, but Herxheimer phenomena were milder and less frequent, indicating that aureomycin may have its greatest use in the treatment of cardiovascular and central nervous system syphilis. Of 11 pregnant women receiving only 30 mg. of aureomycin per kg. per day, for 8 days (1 secondary syphilis, 4 early latent syphilis, 2 late latent, and 4 congenital), all became clinically and serologically negative, and their infants were still negative at 3 months of age. One failure was noted, the mother having received 60 mg. per kilo daily, for only 4 days, ending 2 days before delivery. One other patient on the same regime gave birth to an uninfected child.

Scott<sup>129</sup> considers aureomycin to be second only to penicillin in the treatment of syphilis, but notes that with its use, as with the use of other antiluetic drugs, Herxheimer reactions may follow, and should be thought of whenever an unexplained rise in temperature follows aureomycin administration.

Crowe and Johnson<sup>40</sup> record a case of syphilitic osteoperiostitis, accompanied by a neurosyphilis which was asymptomatic except for a history of epileptic attacks, in which cure followed the administration of 0.75 Gm. of aureomycin 4 times a day, to a total of 50 Gm. The patient showed pigmentation, edema and marked tenderness of both legs, with hard, painful, pretibial nodules, and with a history of recurrent edema of the legs and severe boring pain. X-ray examination showed syphilitic osteoperiostitis of the tibia and fibula bilaterally, and of the left first metacarpal. The diagnosis was confirmed by tibial biopsy. Within 24 hours after beginning aureomycin, a Herxheimer reaction with increase of bone pain occurred but disappeared on continued medication. Two months after discharge, there was noted a decrease in the blood Wassermann reaction, improvement in the cerebrospinal fluid, and improvement in the appearance of the bones. Six months after completion of treatment, there had been continued marked improvement in the CSF, in serologic reaction, and in the bones, and

the patient had been without pain for 4 months. There has been a decrease in the number of grand mal seizures.

Chen, Dienst and Greenblatt<sup>28</sup> suggest that if the effectiveness of aureomycin proves to be equal or nearly equal to that of penicillin, it may prove to be the first satisfactory drug for the fully ambulatory treatment of syphilis. They found that omitting night-time administration did not impair the clinical results in 2 male patients with primary chancre, one having a positive Kahn test. Both ulcers early became dark-field-negative and healed satisfactorily, when aureomycin was given in 1 Gm. doses 4 times daily for 2 weeks. The Kahn test was negative in both cases in examinations made 4 months later. The authors recommend trial of this schedule in other types of syphilis.

Novy<sup>96</sup> has noted that syphilographers have lately been worried because of the apparent tendency of the *Treponema pallida* to develop penicillin-resistant strains, and says that, if this turns out to be true, aureomycin may well prove an important therapeutic aid.

At the present time, aureomycin is not indicated for the routine treatment of syphilis, since clinical work on its administration in this disease is still in the experimental stage, but there is good reason to believe that it will prove in the future to be a valuable member of the group of effective antiluetic drugs.

A cooperative study of aureomycin therapy for syphilis, being carried out under the sponsorship of the United States Public Health Service and the District of Columbia Health Department at Gallinger Municipal Hospital, Washington,<sup>99,134</sup> indicates that aureomycin is therapeutically active, and that doses of 60 mg. per kilo per day for 8 days give better results than this, or a lesser, dosage for shorter periods of time. A daily dosage of 30 mg. per kilo, in divided doses at 4-hour intervals, causes the spirochetes to disappear from the lesions in 20 to 24 hours. Larger doses do not hasten this process.<sup>134</sup> The recommendations made by the group are that aureomycin should be used at present only for patients for



whom oral administration is desirable and for those who are allergic to penicillin.

It must be emphasized that firm recommendations upon the use of aureomycin in lues cannot as yet be given.

## *Urinary Infections*

In most urinary infections which are refractory to treatment, the basic cause is the presence of urinary stagnation, usually secondary to obstruction. In some cases, the organism may be insensitive to the remedies which have been used, or may have so firmly embedded itself in the deeper tissues as to be inaccessible. In many cases, surgical intervention is advisable. The safety of any operative procedure required will be greatly enhanced by the preoperative use of aureomycin. Its postoperative use can be expected to aid in completion of the cure. Neff<sup>92</sup> has stated that infection persisting postoperatively, and unresponsive to the usual measures, can as a rule be cleared up by aureomycin. The prophylactic use of aureomycin has been recommended in genitourinary surgery on patients with cardiac lesions, to prevent the development of bacterial endocarditis.<sup>88</sup>

Of the presently available chemotherapeutic agents, aureomycin is apparently the best. It is relatively nontoxic, does not favor the development of bacterial resistance, shows enhanced activity in an acid medium, and is excreted in the urine in concentrations approximately 100 times those found in the serum.<sup>42</sup> Since the maximum urinary excretion occurs between the fourth and eighth hours after ingestion of aureomycin, it appears likely that a satisfactory interval between doses should be 6 or 8 hours. The amounts of aureomycin excreted in the urine, when the usual range of oral dosage is employed, are far in excess of those requisite for the inhibition of bacterial growth in most cases of urinary infection,<sup>45</sup> and it has been suggested<sup>44</sup> that a dose of 1.0 Gm. every 12 hours may prove to be sufficient for the average case. The

organisms commonly found in cases of urinary infection, including *E. coli*, are particularly susceptible to the action of aureomycin. Strax and Wright<sup>133</sup> consider aureomycin to be the drug of choice in all serious urinary infections.

Many reports have appeared on the successful use of aureomycin in chronic urinary tract infection. In the majority of these cases, other remedies had previously been tried with unsatisfactory results.<sup>12,31-33,45,47,48,63,73,83,95,118,120,127,150,151</sup>

Pflanz<sup>106</sup> reported that he had treated 37 patients with various infections, by means of aureomycin, and stated that in his view, urinary infections form the outstanding indication for aureomycin therapy. He gave aureomycin to 9 patients, all of whom had previously been treated unsuccessfully. Only 3 were not benefited by aureomycin. In 1 case of periarteritis nodosa, urine cultures became sterile, but the patient died of his underlying illness shortly after initiation of treatment.

An extremely obstinate case of urinary infection has been reported by Abrams and co-workers,<sup>1</sup> in a patient with hyperparathyroidism and nephrolithiasis. Within 24 hours of starting aureomycin therapy, the urine from the right kidney and bladder was sterile, but a heavy growth of *Ps. aeruginosa* was obtained from the left nephrostomy tube. Two weeks later *Ps. aeruginosa* and *E. coli* were found in the urine from both kidneys. Nephrectomy was done, and within 24 hours aureomycin had sterilized the urine. The patient was afebrile within 3 days. Eight months later, the urine was still sterile on culture.

Carroll and co-workers<sup>19</sup> have noted unusually favorable results from the use of aureomycin following transurethral surgery. Treated patients had clear urine within a week, in 9 out of 10 cases. Without aureomycin, persistent pyuria is a very frequent occurrence.

Brettler<sup>14</sup> has reported his experience with aureomycin in 8 cases of obstinate urinary infection, most of them complicated ones. Excellent results were obtained by the use of aureomycin, in

conjunction with relief of obstruction where this existed. The author feels that the cost of antibiotic is more than offset by the reduction in hospital time for these patients.

Rutenburg and Schweinburg<sup>120</sup> treated an unselected group of chronic urinary infections with aureomycin. Most of these had been resistant to other forms of treatment and 20 of the 26 suffered from some type of obstruction. In every case, the clinical symptoms disappeared very rapidly, usually within 24 to 48 hours, regardless of whether the urine had, or had not, become sterile. Permanent sterilization of the urine was obtained in 16 patients. Where infection persisted, clinical signs and symptoms were apt to return after stopping treatment. The authors noted a close relationship between the clinical response of an organism and its *in vitro* sensitivity to aureomycin. Aureomycin was uniformly successful in eliminating from the urine *A. aerogenes*, *E. coli*, *P. vulgaris*, *Staph. aureus hemolyticus* and *Strep. faecalis*. Five out of 11 strains of *Ps. aeruginosa* were sensitive to aureomycin and were cleared from the urine. In 21 monovalent infections, there were 5 failures. One of these was due to *E. coli* and 4 to *Ps. aeruginosa*, the bacteria being resistant to aureomycin *in vitro* as well. The authors later<sup>121</sup> reported their results in a total of 89 patients. The response to aureomycin was excellent, very marked improvement or cure occurring in 73 patients. Of these, 65 were cured by 1 course of treatment; 4 by 2 courses; and 2 by 3 courses. With rare exceptions, the strains of *E. coli*, *A. aerogenes*, staphylococcus, streptococcus and paracolon bacillus were sensitive to aureomycin. The greatest number of resistant strains were found in *P. vulgaris* (4 of 11) and *Ps. aeruginosa* (17 of 35).

Meuser and Haschek<sup>89</sup> found that in 131 cases of *E. coli* urinary infection, only 1 was due to an aureomycin-resistant strain. They found also that aureomycin possessed a somewhat higher activity than chloramphenicol against Gram-positive pathogens. There was a relatively high percentage of organisms which were resistant to penicillin and to streptomycin. In their cases, the relation of

simple infection to mixed infection was approximately 2 to 1.

Brainerd and co-workers<sup>12</sup> gave aureomycin to 14 patients, who had responded unsatisfactorily to other chemotherapeutic agents. In 3 acutely infected cases, symptoms rapidly disappeared and the urine became sterile. The other 11 cases were chronic ones associated with urinary obstruction, and although the urine could be temporarily sterilized in 10 of them, relapse or reinfection occurred in all of the cases which were followed up. However, aureomycin seemed to be able to control the infection in 1 case of hydronephrosis of pregnancy so that the fetus could be carried to term, and in 1 case of obstructive infection so that pyelolithotomy could be carried out. *Ps. aeruginosa* was again found to be the most difficult pathogen to eliminate.

Collins and Finland<sup>22</sup> selected 16 adults, most of them in the older age groups, for treatment with aureomycin. Ambulatory treatment was used in 12 cases. All except 1 had a chronic infection which had failed to respond to therapy. Almost all had a long history of severe complicating factors and chronic obstruction. The 1 acute case had not previously been treated and was an acute pyelonephritis complicating pregnancy. Symptomatic relief and bacteriologic cure followed the administration of aureomycin to this patient. While symptomatic and bacteriologic results were good in most of the other patients, improvement could not be maintained because of continued urinary stagnation.

Pyelitis and cystitis occurring in pregnancy have a tendency to become chronic. During gestation there is some dilatation of the ureters, and of the pelvis and calyces of one or both kidneys, ranging from a very slight expansion to a high degree of hydronephrosis and hydroureter. As a result of this, urinary stasis occurs in the dilated portions and predisposes towards infection of the entire system. The so-called pyelitis of pregnancy, which occurs in about 2 per cent of pregnant women is, therefore, actually a pyeloureteritis or pyelonephritis. Infection is most likely to appear toward the latter part of pregnancy, its frequency increasing as pregnancy ad-

vances. The organism most commonly found is *E. coli* (90 per cent); but streptococcus, staphylococcus, *P. vulgaris*, *S. typhosa* and *paratyphosa*, gonococcus, *M. tuberculosis*, or aerogenic coliform bacilli may also be present. Such an infection is of serious prognostic import for mother and child.

For these patients aureomycin has the great advantage that its high effectiveness, excellent tolerance and absence of allergenic properties permit long-term treatment at moderate dosage until delivery occurs. If lengthy treatment should be necessary, it is advisable to give the patient adequate vitamin B complex supplementation.

Gratifying response to aureomycin has been observed in both acute and chronic infections of the urinary tract occurring in pregnancy, but since the original cause of stasis persists until delivery, relapse may occur if treatment is discontinued.<sup>32,50,58,73</sup>

Hartl<sup>61</sup> believes that, in most cases of pyelitis and cystitis in the female, sulfonamides are adequate for recovery but that in certain resistant or severe cases, and in the presence of sulfonamide sensitivity, or of liver or kidney damage, aureomycin should be used. He mentioned 3 cases in which he has employed aureomycin satisfactorily. One was a case of pyelitis in a woman who was 8 months pregnant, and who had suffered a relapse in spite of sulfonamide therapy. After 4 Gm. of aureomycin, she was completely free of fever and the urine culture was sterile. A second patient, in the ninth month of pregnancy, who had a severe pyelonephritis and was sensitive to sulfonamides, recovered after 8 Gm. of aureomycin. A third case, with a congenital cystic kidney the size of a child's head, and pregnant 3 months, developed severe *E. coli* pyelitis with chills and fever. After the administration of 8 Gm. of aureomycin in 5 days, she was without pain or fever and the leukocyte count and urinary findings were normal. Previous treatment with penicillin had been completely ineffective.

Cordonnier<sup>36</sup> noted that aureomycin has been found to give results superior to those following sulfonamides, in the treatment

of chronic renal disease due to congenital anomalies. In describing a case of congenital "urethral valves," Cordonnier commented that these abnormal structures in the posterior urethra may or may not be demonstrable cystoscopically, because the visible field in a child is very limited.

Campbell<sup>18</sup> discussed obstruction of the lower urinary tract in children and stated that the congenital anomalies usually responsible for this pathology are stenosis of the external meatus and contracture of the vesical outlet, although stenosis of the prepuce, "valves" in the prostatic portion of the urethra, hypertrophy of the verumontanum, urethral and prostatic tumors, and neuromuscular disease may at times be responsible. The possibilities of secondary calculus formation and blockage, localized suppurative lesions, and injury to the kidney are considerations of vital importance. Campbell stated that complicating infection can be anticipated in every case, and often is of itself fatal. The therapeutic corollary is that even though the obstructing lesion is removed, the patient cannot be considered cured until the urine has been sterilized.

Wiesel and McManus<sup>139</sup> described a necrotizing renal papillitis which may present an obstacle to the satisfactory management of diabetes. Most cases have been diagnosed postmortem. Extensive involvement may be responsive to aureomycin and some cases of unilateral disease can be treated surgically with success.

Banks and Hill<sup>8</sup> called attention to the possibility of reflex anuria secondary to unilateral ureteral obstruction by calculus, and taking the form of a lower nephron nephrosis. They cited a case which had a stormy and prolonged course before the cause of the anuria was corrected, but which apparently was protected from infection by prophylactic aureomycin administration.

Rubin and Goldstein<sup>118</sup> chose 25 of their most refractory chronic cases for a trial of the efficacy of aureomycin. Very gratifying results were obtained in this group, none of whom had benefited from any previous form of medical or surgical treatment. The authors characterized the response as excellent in 9, good in 4,

good but temporary in 7, poor in 5. Recurrence or persistence of infection was observed in all cases with urolithiasis.

*Infections of the Upper Urinary Tract*—Cystitis, ureteritis and pyelonephritis (or, as it was formerly known, pyelitis) are probably always secondary to infection of the lower urinary tract or of other body tissues. The route of invasion may be hematogenous, lymphogenous, or ascending; extension from nearby infected structures is not infrequent. When treatment with the antibiotics, or sulfonamides, or combinations of these agents, does not produce cure, a careful search for extra-urinary foci of infection must be made, and will often require the assistance of several consultants.

In general, it may be said that acute infections of the upper urinary tract yield readily to aureomycin therapy. In patients with acute pyelonephritis, alone or with cystitis, there is almost invariably sterilization of the urine following the administration of aureomycin by mouth.<sup>12,32,42,59,60,63,69,73,133</sup> As a rule the symptoms are controlled, and pyuria abolished, within 1 to 4 days.<sup>12</sup>

Douglas and co-workers<sup>44</sup> reported clearing of pyuria, disappearance of symptoms, and return to normal temperatures within 72 hours, in 17 patients with *A. aerogenes* infection, 8 with streptococcal, 6 with staphylococcal, and 34 of 44 with *E. coli* infection. Similar results were obtained in 5 cases of *Ps. aeruginosa* invasion; although growth-inhibition required high concentrations *in vitro*. The authors note that *in vitro* tests give at best only a rough indication of sensitivity and probable clinical response. Good results were observed in 3 of 8 cases infected with *P. vulgaris*. In 19 other cases, *P. vulgaris* appeared in the urine after the original pathogens had been eradicated, but in most uncomplicated, unobstructed cases, the urine later became spontaneously sterile.

*Infections of the Lower Urinary Tract*—In the male, when the urethra or the prostate is the site of acute infection, it is always necessary to rule out gonorrhea.

Any factor, such as alcoholism, which lowers the resistance of the urethral mucosa, may permit the development of infection, as

a result either of invasion from without, or of the development of pathogenicity in the normal urethral flora, or of extension of infection from the upper urinary tract.<sup>52</sup> An apparently cured attack of gonorrhea may be followed by nonspecific urethritis caused by invasion by other organisms.

**CYSTITIS**—Abacterial pyuria, or acute interstitial cystitis, is recognized as a fairly common acute condition, presumably of virus origin and, in the male, probably arising in the prostate or prostatic urethra, although there is frequently no history of lower urinary tract disease.

Coutts and associates<sup>37</sup> state that acute interstitial cystitis can also be caused by fungi, spirochetes, protozoa or metazoa, and that meticulous examination of the urinary sediment will frequently identify the agent. Lymphogranuloma venereum is a more common cause, they believe, than would be expected, and the Frei test should form a part of the diagnostic procedure. They note also that in a number of cases which are apparently bacterial in nature, the bacterium is a secondary invader, complicating the original abacterial infection. The latter tends to persist after removal of the presumed pathogen. If inadequately treated, it may persist or recur for years, and may then either be asymptomatic or cause much discomfort and annoyance.<sup>37</sup> Until recently, intravenous arsenicals and intramuscular penicillin were used, the infection usually being controlled in 3 to 6 weeks.

Baurys<sup>6</sup> gave aureomycin with spectacular results to 2 patients with abacterial pyuria. Although pyuria persisted for a few days, both patients became almost free of symptoms overnight, and no recurrence appeared during several weeks of observation. The author remarks that the dramatic response of these 2 patients far surpassed those which he had previously observed with any other form of treatment. Hankey and Stept<sup>59</sup> also reported striking relief of symptoms, clearing of the urine, and healing of the bladder and urethra following the use of aureomycin for abacterial pyuria.

Morisani<sup>91</sup> has reported the case of a nine-month-old baby suf-



fering from cystitis accompanied by fever, vomiting and diarrhea. No benefit followed the use of penicillin, sulfonamides or streptomycin. All treatment was suspended for 48 hours, and aureomycin was then given rectally. After 3 days' treatment, the fever dropped and examination of the urine showed it to be practically clear.

**URETHRITIS**—Nongonorrheal urethritis may be produced by a variety of bacteria; by viruses and similar pathogens, including the organisms of granuloma inguinale or lymphogranuloma venereum; and by pleuropneumonia-like organisms.

Chen and Dienst<sup>25</sup> point out that nongonorrheal urethritis is not rare, but actually constitutes a major problem for the urologist, and note that they have successfully used aureomycin in this condition. Aureomycin has been referred to as the drug of choice in abacterial urethritis.<sup>109</sup>

Pleuropneumonia-like organisms have been observed by Brown and co-workers<sup>15</sup> to disappear from the genital tract of patients given aureomycin orally. Rheumatic disease, which was also present in a number of cases, improved both subjectively and objectively. Since aureomycin is spirochetostatic, the possibility of co-existing syphilis should always be borne in mind when treating cases of urethritis.

Durel<sup>46</sup> treated 16 cases of viral urethritis with aureomycin, obtaining cure in 6, striking improvement in 6 and lack of response in 4. At his request, one of his colleagues made a similar study in 51 patients, obtaining cure in 30, improvement in 11 and failure in 10. Durel considers that in aureomycin we have a weapon of great value against urinary infection due to viruses, or virus-like organisms.

Hook<sup>68</sup> has reported a case of polyarticular rheumatism and genitourinary infection caused by pleuropneumonia-like organisms (*L. organisms*), which was cured, as to both the rheumatism and the urinary infection, by means of aureomycin.

*Trichomonas vaginalis* has been recognized for 114 years as a frequent pathogen in the female genital tract. Nearly 50 years ago, it

was realized that trichomoniasis could also be a cause of genito-urinary infection in the male, but this was believed to be quite rare. More recently, however, the incidence of this infection in men has been found to be fairly high, and it has even been suggested that it should be regarded as the seventh venereal disease, if genital infection by Vincent's organism is considered as the sixth. McVay and co-workers<sup>86</sup> note that in various studies the incidence of trichomonas infection in the husbands of infected women has been from 25 to 80 per cent. The infection is often a mixed protozoal and bacterial one. *Trichomonas* invades the prostate and seminal vesicles in about 1 per cent of these cases. Since the authors knew that intravaginal aureomycin was effective in the female type of infection, and since aureomycin is excreted in large amounts in the urine, they gave 3 Gm. of oral aureomycin daily for 3 days and then 2 Gm. daily for 4 days, to 2 men having this type of infection in the urethra, and observed disappearance of all signs and symptoms within a week. The authors then extended their survey to include 9 additional patients, with similar results. Whenever possible an infected wife was also treated. Symptoms of trichomoniasis disappeared inside of a week in all; returned 3 weeks later in 1 case. The recurrence was considered to be due to reinfection. In another patient, examined 6 months later, the organism was demonstrable in the prostatic secretion, but there was no other evidence of infection. The authors believe that a satisfactory criterion for cure in the male would be failure to demonstrate the organism in any of 4 weekly examinations, prostatic massage being done at 2 of them.

The action of aureomycin on trichomonads seems to be more than a mere inhibition of growth. Shaffer and Biegeleisen<sup>11,130</sup> found that a concentration of 0.059 mg. per cc. produced a moderate reduction in the number of *T. hominis* in the culture after 24 hours and a marked reduction at 48 hours, while a concentration of 0.236 mg. caused complete disappearance of the organism in 24 hours.

# CHAPTER THREE

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## INFECTIONS PRIMARILY INVOLVING THE SKELETAL SYSTEM

THE problem of infection of the skeletal system has always been a grave and urgent one. Whether in bone or in joint, the confinement of the infectious focus within unyielding walls causes vascular obstruction, toxicity and severe pain; while involvement of the supportive structures of the body causes this type of disease to be severely incapacitating. The difficulty of ensuring free drainage and complete eradication of infected tissues produces a tendency toward chronicity, with resultant continued ill health, and the ever-present danger of a sudden overwhelming of weakened body defenses by fatal septicemia. The world literature for the past 5 years has borne eloquent witness to the value of aureomycin—alone in acute infections, combined with surgery in more chronic ones.

### *Infectious Arthritis*

The use of antibiotics in no way lightens the responsibility of the physician to follow accepted methods for the clinical management of infectious arthritis. The surgeon's responsibility has actually increased, since he must exercise even greater vigilance than formerly in watching for the symptoms and signs of joint infection, often masked to some degree by antibiotic treatment.

Many early acute cases of infectious arthritis will clear up when aureomycin is given, but a number of them will require evacuation

of the joint, by aspiration or drainage. Evacuation will almost *always be necessary in chronic infections*. VARIDASE\* Streptokinase-Streptodornase Lederle may prove highly useful for the liquefaction of purulent exudates to permit thorough drainage. Where long-continued pain and septic absorption have lowered the patient's resistance, attention must be paid to his general nutrition. A highly nourishing diet, with vitamin supplementation, should be given, and blood transfusions are often of great value. For high-potency supplementation of the diet, PERFOLIN\* Multivitamins Lederle may prove most useful.

In undulant fever, joint involvement is frequent and may be the chief cause of complaint. Janbon and co-workers<sup>15</sup> have reported 3 cases of brucella osteoarthritis of the coccyx, and have found prolonged administration of aureomycin, combined with intravenous vaccine therapy, to be the most satisfactory form of treatment. Stoffel<sup>32</sup> observed rapid cure of spondylitis occurring in the course of brucellosis, when the disease was treated with aureomycin.

Löffler and Moroni<sup>19</sup> describe the case of a young man who, about 2 weeks after drinking large quantities of raw milk, developed pain in the back, chills and fever. He was found to have severe acute brucellosis with spondylitis. Treatment with a combination of aureomycin and streptomycin halted the progress of the spondylitis, and cleared up all other signs of infection. The authors further mention the case of a 6-year-old boy, in whom Perthes' disease (osteochondritis of the hip joint) had been diagnosed 2 years before. At the time of his birth, the child's mother had been suffering from a very severe attack of brucellosis, which had probably existed during the whole of her pregnancy. The boy's hip disease was considered by the authors to be of brucellar origin, although agglutination and complement-fixation tests were negative; but it might very well have been an "embryopathia," such as is seen after rubella and certain other infectious diseases. Today, diagnosis of brucellosis in the mother during pregnancy, and ade-

\*Reg. U.S. Pat. Off.



quate treatment by means of aureomycin, would probably avert severe joint damage of this type.

Eales<sup>8</sup> has reported the case of an eleven-year-old boy, who was in good health until the sudden development of pain in the hip, with limping. A week later, he became feverish and easily fatigued. This condition lasted for some weeks and was believed to be due to tuberculous joint disease. The hip was immobilized in plaster and the patient admitted to hospital. Remittent fever persisted, and blood cultures were found to be positive for *Brucella melitensis*. The boy was given aureomycin for 5 days. Fever disappeared, and free movement returned to the hip. The patient had not begun weight-bearing, when suddenly, a week after aureomycin was stopped, severe pain and swelling developed in the opposite hip, and fever returned. Aureomycin and streptomycin were given for 3 weeks. Within 48 hours after the first dose, the pain began to decrease and the temperature subsided. Recovery thereafter was uneventful, and the patient was discharged about 6 weeks after the beginning of the second antibiotic course, walking well and apparently cured.

When *H. influenzae* localizes, the site of preference appears to be the meninges. Very few cases of joint involvement have been reported and, in 50 per cent of these, meningitis was also present. This combination of involvements has up till now been uniformly fatal in the reported cases. Joslin and Howard<sup>18</sup> gave aureomycin to an eight-month-old child with *H. influenzae* infection of both elbows and upper respiratory infection. On admission, the child was given penicillin; but on the fourth day, culture of the joint fluid was reported as yielding *H. influenzae*, type B, and on that day, signs of meningitis developed. Spinal fluid culture was also positive for the organism. Aureomycin was substituted for penicillin and on the next day, the temperature reached normal for the first time, although evidences of meningitis persisted. Three days later, chest X-rays showed bilateral pneumonia. A change from oral to intravenous administration of aureomycin was made and

produced symptomatic improvement. Very little swelling of the elbows remained, although there was still considerable pain. Two days after intravenous aureomycin had been started, the spinal fluid culture became negative for the first time. After 80 hours of intravenous aureomycin, oral administration was resumed. Gradual recovery took place and the child, 5 months after discharge, was in good physical condition, although his development was slightly retarded and there was some limitation of movement in 1 elbow joint. The authors suggest that in a case of this severity, initiation of treatment with intravenous aureomycin might have given prompter response and, consequently, more complete recovery.

Shwachman and associates<sup>30</sup> have reported the case of a seriously ill child with purulent *Staph. aureus* arthritis, responding favorably to aureomycin. Isolation of the organism showed it to be resistant to penicillin.

Two severe cases of arthritis and septic osteomyelitis have been reported by Neff.<sup>25</sup> Infectious involvement of the hip in a three-year-old girl was unaffected by penicillin and sulfonamides. The child's general condition was gravely septic, with high fever, meningismus and electrocardiographic evidence of toxic myocardial damage. Five days after starting aureomycin, in addition to penicillin, the temperature had dropped and the child's condition was definitely improved. The myocardial involvement remained evident for several weeks but finally subsided. After 3 months, the hip disease appeared completely cured, roentgenologically and functionally, and the electrocardiogram had returned to normal. The second case reported by Neff was similar but less serious, involving the ankle joint in a seven-year-old child. The only surgical measure required during aureomycin therapy was immobilization of the joint in a plaster cast. Neff remarks that such a procedure would have been absolutely unthinkable before the antibiotic era. The child made a prompt and full recovery.

Ord<sup>26</sup> notes that, before the antibiotic era, the chief emphasis

in the treatment of suppurative arthritis was placed on aspiration of the joint and immobilization, whereas the aim today is to maintain a sustained therapeutic concentration of the indicated antibiotic at the site of infection. Aureomycin proved extremely satisfactory in 1 case of suppurative arthritis of the hip, after the complete failure of penicillin.

In an article on his own experience with antibiotics, Perruelo<sup>27</sup> cites a case treated by Kohn. The patient, a young man suffering from acute arthritis of the hip following an attack of grippé, received large doses of penicillin without benefit. When moderate dosage of aureomycin was added to the penicillin treatment, improvement was rapid and striking, with prompt disappearance of pain and fever. The limb was immobilized and by the end of a month the acute infection had disappeared.

## *Compound Fractures*

Compound fractures are among the most important and frequent injuries seen by the physician, either in war or in peace. Infection of the bone is a very frequent complication. In view of the serious and often intractable nature of osteomyelitis, antibiotic therapy is mandatory. Emergency treatment consists in control of hemorrhage, prevention of further contamination, and provision of support to the injured limb sufficient to prevent increased damage to the bony or soft tissues. The administration of aureomycin or other available antibiotic should probably be started at this time.

The cardinal surgical principles involved in the care of compound fractures are: prevention of further local injury; relief of shock; careful debridement; and reduction and immobilization of the fracture. Aureomycin has turned the scale in a number of apparently hopeless cases. It reduces the incidence of osteomyelitis in compound fractures and frequently makes possible primary repair of torn tendons.<sup>5,20,22,34</sup>

The fact that no one antibiotic can be expected to be always

effective, even when the organism is one which is usually sensitive, is underlined by a case reported by Mascart and Dejardin.<sup>23</sup> After reduction of an oblique fracture of the femur, the patient became feverish and toxic, in spite of high dosage of penicillin and streptomycin, and suppuration developed at the level of the operative wound, culture giving a coagulase-positive staphylococcus. The organism was only slightly sensitive to penicillin, completely resistant to streptomycin, but strongly sensitive to terramycin, which was then begun. X-rays taken at that time showed a beginning osteitis. Gradual improvement took place during the following 10 days, but relapse followed. The organism was found then to have become relatively resistant to terramycin but sensitive to aureomycin. Treatment with the latter produced cure.

## *Osteomyelitis*

The increasing use of aureomycin for infections anywhere in the body, and its prophylactic employment in many cases of compound fracture, have greatly reduced the incidence of osteomyelitis.

Early cases of osteomyelitis without extensive bone destruction will often respond to aureomycin alone.<sup>17,37</sup> Chronic bone infection, or X-ray evidence of osteitis, or the development of a sequestrum, is an indication for surgery; with thorough removal of necrotic material, devitalized bone, and surrounding scar tissue. Satisfactory and often remarkable results have been obtained with aureomycin in stubborn or chronic cases which were resistant to all previous attempts at cure.<sup>1,3,4,5,9,14,17,22,24,25,29,30,31,33,34,35</sup> VARIDASE may prove useful for enzymatic debridement.

The tendency of penicillin to permit the development of resistance in staphylococci is well exemplified by the experience of Basu.<sup>2</sup> Using penicillin in cases of osteomyelitis, he obtained healing in a reasonable period in only about 63 per cent of cases, 22 per cent requiring more than 6 weeks. In 13 per cent, more than 1 operation was required. He therefore decided to try aureomycin

in 30 chronic cases, together with indicated surgical and supportive treatment. The drug was started 24 hours before operation and administered for 8 or 10 days afterwards. It was well tolerated and there were no untoward effects. At operation, aureomycin powder was insufflated into the diseased areas whenever possible, in order to bring the drug into better contact with the infected tissues. The initial healing of the wounds was eminently satisfactory, over 90 per cent of the cases healing soundly in 4 weeks, and no case having a true recurrence. These results constitute a definite improvement on those obtained with penicillin, or with penicillin and streptomycin combined. The author was much struck with the simplicity of the treatment and the rapidity of the cure.

DeWinne and co-workers<sup>7</sup> state that, in osteomyelitis, aureomycin acts more rapidly than penicillin on the pathogens, prevents massive liberation of toxins which may dissolve bony tissue, and permits the leucocytes to clear up the pus. Any sequestrum present, being then in an aseptic field, behaves like a bone graft. In this way, aureomycin may be able to replace formerly indispensable surgical procedures. The authors report the case of a five-year-old child with *Staph. aureus* bone infection, who remained in good general condition under massive dosage of penicillin, but whose osteomyelitis progressed. A Brodie's abscess formed, and there was extensive destruction of the diaphyseal bone of the elbow, fracture and early sequestrum formation. Aureomycin was added to the existing therapy and 3 weeks later the abscess had cleared and bone healing was accelerated. Five months after beginning aureomycin, the bone had become completely reconstituted.

Jentzer<sup>16</sup> has reported 2 cases of penicillin-resistant osteomyelitis treated with aureomycin. One was that of a thirteen-year-old boy who about 5 weeks previously had scraped his right leg. The illness began with high fever, but there was no apparent cause for the rise in temperature, except for a small ulcer on the right knee and an enlarged inguinal gland. The swelling of the gland disappeared following local application of an ointment, but the boy

began to complain of sharp pain in the right tibia. Fluctuation was absent, but there was marked tenderness to palpation. Sulfonamide and penicillin treatment brought no improvement. The parents were told that operation would probably be necessary, but that before operating the author would like to try a treatment which might cure the boy without surgery. Aureomycin was begun and was followed by an abrupt drop of temperature within 48 hours and complete disappearance of clinical manifestations. Eight days later, the child left the hospital cured, and was still well a year later. The other patient was a fifteen-year-old boy who fell from a tree on to his flexed wrist. He suffered pain for about 5 minutes, and was then able to go on working. Two days later, the forearm became painful and swollen, and compresses did not help. No fracture was seen by X-ray. Penicillin, streptomycin and sulfonamides were then given and a fluctuant area on the ulnar aspect was incised, yielding 40 cc. of pus from which *Staph. aureus* was cultured. The boy left the hospital at his parents' request, well on the way to cure, but less than a month later he returned, with evidence of recurrence. X-rays showed osteomyelitis of the ulna, involving the lower two-thirds of the bone, with considerable periostosis, and a fracture of the distal third. Penicillin and streptomycin for 4 days brought no improvement, and aureomycin was begun. Strength slowly returned to the hand, and an X-ray taken a month later showed striking evidence of repair and healing of the fracture; the spicules of periostosis had almost disappeared and the fusiform swelling of the bone had sharply diminished. Improvement continued, and all treatment was stopped about 3 months later, after a total dose of 630 capsules of aureomycin (250 mg. each). The boy left the hospital in excellent health, local and general, and with only slight limitation of elbow extension and flexion.

In both the above cases, operation, which at one time seemed clearly indicated, was unnecessary. The author feels that aureomycin has completely modified the prognosis of osteomyelitis,

whether acute or chronic, and believes it to be the ideal medication for this disease. He warns, however, that entire dependence should not be placed on any antibiotic, however good, but that every effort should be made to strengthen the patient's resistance.

Rutenburg and associates<sup>28</sup> obtained gradual healing following the use of aureomycin in 2 cases of chronic osteomyelitis, one of them in a patient with peripheral vascular disease complicated by ischemic arteriosclerotic ulcer. Previous treatment with penicillin and streptomycin had failed. They also obtained good results in one acute case of osteomyelitis, and doubtful improvement in a case of wound infection and osteomyelitis following hip-nailing. In this last case, the invading organisms were resistant to penicillin and streptomycin. Although these organisms were removed, they were replaced by *Ps. aeruginosa* and a nonhemolytic streptococcus.

Wright<sup>36</sup> has reported the case of a seven-year-old girl from Port of Spain, Trinidad, with acute hematogenous osteomyelitis, which developed about one month after a large alveolar abscess. In spite of penicillin and surgery, her condition grew continually worse, and amputation was advised. A Trinidad physician, who was about to return home from the United States, was asked to bring some aureomycin, in the hope that it might prevent amputation. Administration of 1 Gm. daily for 8 days produced spectacular improvement, with subsidence of pain. The child was flown to the United States, after more than 3 months of illness, for further treatment. Aureomycin was continued in the same dosage, and she was given a high protein diet with vitamin supplements. The elevated temperature and rapid pulse returned to normal after 19 days of treatment, and 3 months after admission X-ray evidence of healing was noted. Two months later, bone healing was complete, and sequestrectomy was not required. A brace was ordered for the child at the time of discharge from the hospital, to prevent injury to the weakened tibia, but recovery was so satisfactory that the brace was soon dispensed with.

Goldner and Gailey<sup>11</sup> have used aureomycin in the treatment

of 26 patients with chronic osteomyelitis, in whom other antibiotics had either been ineffective or had lost their effectiveness, and have followed 15 of them for one year. The series included 4 patients with chronic osteomyelitis, on whom adequate surgery could not be performed. In this group, treatment failed in 1 case of tuberculosis of the shoulder with severe purulent secondary infection, the patient dying of miliary tuberculosis. One case of chronic osteomyelitis of the sacrum and pelvis, with sinus formation, had been unaffected by penicillin, streptomycin, or the sulfonamides. After a year of illness, aureomycin treatment was started and was able to control the exudate. Recurrence was observed each time that aureomycin was stopped. Another patient had chronic osteomyelitis of the coracoid process and body of the scapula. Excision of the sinus tract and administration of penicillin did not stop drainage. Following aureomycin administration, exudation ceased, and did not recur during 9 months of observation. The fourth patient was an elderly man with osteomyelitis of the tibia and some circulatory impairment, who was suffering severe pain. Aureomycin relieved the pain, cleared up the cellulitis, and lessened the drainage. Amputation had been seriously considered but was put off indefinitely in view of the satisfactory control with aureomycin. Seven patients were subjected to surgery and given aureomycin as additional treatment. Results were apparently better than with penicillin, but the authors feel that they cannot estimate the part played by aureomycin, since surgery was also used. Four patients with chronic osteomyelitis required amputation, aureomycin being given before and after operation in 3 cases. The fourth patient, whose infection was due to *Staph. aureus* received no benefit from penicillin (preoperatively and postoperatively), or from streptomycin, but when aureomycin was begun, healing occurred within 6 weeks. The remaining 11 patients were not followed long enough to permit evaluation of the results.

Until recently, few surgeons would have dared to attempt bone grafting in the presence of infection, and even fewer would



have used bone grafts in the treatment of chronic hematogenous osteomyelitis. However, during World War II, the large number of compound fractures, the high incidence of chronic bone infection, and the availability of effective antibiotic agents, led some to attempt bone grafting. Bickel and Bateman<sup>3</sup> have used bone grafts in 14 patients with osteomyelitis of long standing, with success in 11. Eleven of the patients were treated with penicillin and 2 with streptomycin. The fourteenth patient had chronic osteomyelitis and nonunion of the upper femur, following an infected osteotomy. *Staph. aureus* was cultured from the pus and was found insensitive to penicillin or streptomycin, but very sensitive to aureomycin. Aureomycin was administered, the wound was saucerized and packed open and, 3 weeks later, the granulation tissue was curetted out. Packing the defect with bone chips and primary closure were followed by apparent cure.

Buchman and Blair<sup>4</sup> have found that use of preoperative and postoperative antibiotic therapy, thorough saucerization, local antibiotic application, and primary closure is an extraordinary improvement on any previous method of treating chronic hematogenous osteomyelitis. The necessity for frequent intramuscular injections when penicillin or streptomycin is used, the very frequent occurrence of serious reactions to these antibiotics, and the increase in the number of resistant organisms caused the authors to study the action of aureomycin. Sensitivity tests showed that practically all of 43 strains of coagulase-positive *Staph. aureus* were inhibited by 1 microgram per cc., or less, of aureomycin, and most of them by 0.39 microgram or less. In 100 saucerization operations, 80 per cent of surgically approachable lesions healed by primary intention, and 10 per cent of the patients healed following additional surgical procedures. In only 3 per cent was there relapse. The authors have therefore modified their practice to permit the oral administration of aureomycin for the 24 hours preceding operation, intravenous aureomycin during operation, and oral aureomycin postoperatively. During closure of the wound, they

use local application of aureomycin solution (0.5 mg. per cc. of saline). No evident discomfort or irritation has followed local application, even in unanesthetized patients. While only a few cases have so far been treated with this antibiotic, several of them appeared to be doomed to failure; and these healed successfully, when aureomycin was substituted for penicillin or streptomycin.

Ingelrans and co-workers<sup>13</sup> observe that, while immobilization in a cast and penicillin administration still form the accepted method of treating acute osteomyelitis, and usually have an excellent effect on the general condition, their influence on the local lesion is less constant. Complete or partial failure may follow, as in 2 cases described by them. One girl, 12 years old, with osteomyelitis of the foot, *Staph. aureus* septicemia and pericarditis, responded not at all to penicillin. The organism was found to be resistant to penicillin and streptomycin, but sensitive to aureomycin, which was then given in a dosage of 2 Gm. daily for 36 days. When the drug was stopped, the slow, steady improvement which had been taking place halted and a month later the disease began to progress. A second course of aureomycin brought about cure, after removal of a sequestrum under aureomycin protection.

The other patient was a seven-year-old girl, with osteomyelitis of the tibia, which had persisted for 1 month in spite of immobilization and penicillin therapy. Aureomycin was given for 35 days and rapidly banished fever, but had little effect on the X-ray picture. A second course brought about progressive disappearance of the lesions.

Ingelrans and Breton<sup>12</sup> reported cure of an acute osteomyelitis, complicated by bullous pneumopathy, by means of combined therapy with penicillin, streptomycin and aureomycin.

Occasionally, osteomyelitis may develop in a fulminating form, and such cases require early and intensive therapy, sometimes with a combination of remedies. LoPresti<sup>21</sup> has reported one such patient who, 24 hours after onset, was in peripheral circulatory collapse, with a temperature of 103° and a widespread urticarial rash.

There was generalized abdominal pain, marked pain on passive movement of the right knee, delirium and semistupor. Transfusion, adrenal cortical extract, Benadryl and a sulfonamide were given and intravenous fluids were administered continuously. Remarkable improvement took place by the next day, but a septic temperature still remained and there was evident localization of infection in the right knee. *Staph. aureus* was cultured from the blood stream. The organism was found to be sensitive to penicillin and very sensitive to aureomycin. Chloramphenicol and the sulfonamide were therefore stopped and aureomycin was given instead. Evidence of systemic infection had disappeared by the seventh hospital day, and local manifestations subsided gradually. The patient was discharged on the twenty-fifth hospital day, with complete range of motion in the knee and almost complete disappearance of any evidence of infection.

While, from the nature of the route of infection with actinomycetes, the mandible is the bone most frequently affected, there are cases on record in which the bones of the limbs were involved. Cope<sup>6</sup> states that the spinal column is attacked often enough to require that it be kept in mind in the differential diagnosis of spinal disease. In most cases, large doses of penicillin, continued for as long as several months and occasionally for more than a year are required; but, if the organism is not sensitive to penicillin, then Cope advocates the use of aureomycin or similar antibiotic.

The bone marrow may be involved in brucellosis, appearing as focal granulomatous lesions. Fisher<sup>10</sup> has reported improvement following the use of aureomycin in one such case.

## CHAPTER FOUR

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## INFECTIONS PRIMARILY INVOLVING THE NERVOUS SYSTEM

THE widespread and rapid diffusion of aureomycin into all tissues and fluids of the body, and in particular its ability to pass the meningeal-blood barrier, make it of great value in the management of infections of the central nervous system. Orally administered, it appears in the cerebrospinal fluid in most cases within 24 hours, and within about 4 hours when given intravenously. In general, the levels increase proportionately to the increase in serum concentration, and do not appear to be much influenced by the presence of meningeal inflammation.

Infection may reach the brain tissue, or the meninges, either by way of the blood stream, through the lymphatics, or along the axis cylinders of the nerves; or it may be introduced from without by penetrating injuries to the skull. Prompt and adequate treatment of all cases of infectious disease in any part of the body, even where these appear to be of minor significance, is the best prophylaxis against extension to the nervous system. The high mortality attendant on infection of the central nervous system, and the possibility of mental and physical crippling in surviving patients, make it imperative to employ in such infections the best therapeutic means at our command. For this purpose, the wide therapeutic range of aureomycin points to it as the indicated antibiotic in the great majority of cases.

## Brain Abscess

The organisms most frequently responsible for brain abscess are the common pyogenic types, *Staphylococcus aureus*, *albus* and *pyogenes*, hemolytic streptococci and pneumococci, but many other varieties may be found. In brain abscess following otitis media, there is often little or no meningitis, general spread of infection being prevented by adhesions. Chemotherapy and surgical drainage is the treatment of choice. Aureomycin has been effectively used in the treatment of a number of cases of brain abscess.<sup>47,48,79</sup>

Mansuy and Chavanne<sup>49</sup> have reported a case of temporal abscess draining spontaneously into the mastoid, in which the presence of a huge collection of pus produced few signs or symptoms. The patient complained only of fetid discharge from the right ear, which had lasted for several months. On questioning, he gave a history of the appearance, in succession, of diffuse headache, personality changes, excessive fatigability and occasional periods of very deep sleep. When exposed at operation, the entire mastoid area was found to be necrotic, and in the anterior portion of the aditus, there was pus mixed with brain matter. Exploration showed the existence of an extensive temporal abscess opening into the mastoid. Persistent foci of infection necessitated 3 more surgical interventions, and it was necessary to use intensive supportive and antibiotic measures to carry the patient through his stormy convalescence. The results of administration of penicillin and streptomycin were not satisfactory, but prompt response was obtained when aureomycin was added to the regimen. However, it was not until the last area of infection was opened and drained that aureomycin was able to bring about complete cure. The authors emphasize that no one method of attack, surgical, antibiotic or supportive, would have been sufficient by itself to obtain this result.

In a similar case reported by Elsen and co-workers,<sup>21</sup> therapy

with penicillin and aureomycin rendered the patient afebrile and controlled the spread of infection. Following adequate surgical treatment of the brain abscess, improvement was steady and dramatic. Penicillin and aureomycin were given postoperatively, and the wound was irrigated daily with a solution of penicillin and streptomycin.

Schneider and Hegarty<sup>68</sup> have discussed the possibility of extradural hemorrhage as a complication of infections in the nose and ear. They report the case of a young man who began to show signs of temporal lobe pressure, 5 weeks after the appearance of a furuncle on the nose. Recovery had apparently been complete, until the onset of fever, somnolence, headache and mental confusion, 5 days before admission. A tentative diagnosis of brain abscess was made, and an electroencephalogram confirmed its location in the right fronto-temporal lobe. Aureomycin controlled the fever, but somnolence increased. At operation, bloody material with a grayish tinge was found, and the regional bone was necrotic. Cultures yielded hemolytic *Staph. aureus*. Postoperatively the patient was given aureomycin, penicillin and sulfadiazine. Convalescence was rapid and uneventful. Nearly 6 months later, the patient was re-admitted for cranioplasty and at this time revealed signs of focal epilepsy. Operation had to be deferred on account of an attack of sinusitis and the patient was maintained on anticonvulsants until cranioplasty could be performed a couple of months later. He was discharged neurologically negative and given maintenance anticonvulsant treatment.

Kufner and Schütz<sup>39</sup> report a case of pneumococcal meningoccephalitis and brain abscess, with rupture into a lateral ventricle, associated with bilateral otitis of 2 months' duration. The patient became so much worse that he was bedridden on account of increasing headache, and twice lost consciousness. When he was admitted to the hospital, meningeal signs predominated, and were rapidly improved by intensive penicillin dosage. Investigation, however, showed severe mastoid involvement, and operation was

considered imperative. At operation, a large, poorly encapsulated brain abscess was exposed and drained. The temperature rose after operation and, although the patient seemed better under penicillin treatment, the spinal fluid findings became worse and the meningeal reaction increased. Some clinical improvement followed the addition of a sulfonamide, but was unaccompanied by objective improvement. In spite of the addition of streptomycin to the previous medication, the patient went rapidly downhill and, little more than a week after operation, appeared to be in a hopeless condition. In view of the possibility of another abscess, he was re-examined. In the depths of the abscess cavity could be seen a perforation into the lateral ventricle, opening and closing with each pulsation. The patient had grown worse in spite of treatment with sulfonamides, streptomycin and penicillin in sufficiently high doses to produce good CSF penicillin concentrations, and penicillin irrigation of the abscess cavity. It was obvious that none of these remedies was able to attack the particular pneumococcus involved, whether because of the innate or acquired resistance of the organism, or its inaccessibility. A different approach was obviously demanded; and, after consultation between neurologist, otologist and internist, peroral aureomycin therapy was begun. The daily administration of 1.5 Gm. of aureomycin produced a drop in fever and amazing improvement in the clinical picture. After 4 Gm. had been given, the rate of improvement dropped off. The dosage was increased, and after the administration of a total of 8 Gm. of aureomycin in 6 days, healing was practically complete. The spinal fluid findings cleared up, the temperature returned to normal and the obstipation which had been present entirely disappeared. The abscess cavity was clean and the communication with the ventricle had begun to close by granulation. On the twenty-ninth day, all specific medication was dispensed with. The only remaining abnormality was a paroxysmal tachycardia persisting for about 12 days.



## *Encephalitis*

Inflammation is rarely confined to the brain tissue alone, but usually affects the spinal cord as well. It would probably be more exact to speak of "encephalomyelitis." The meninges and the peripheral nerves may also be implicated to varying degrees. The majority of cases appear to be of virus origin, although bacterial encephalitis does occur. Brucellar encephalitis is being increasingly reported in the literature.

More than 50 years ago, it was observed that, next to fever, involvement in varying degree of the central nervous system is the most constant feature of brucellosis. Although meningitis and encephalitis occur infrequently, Spink and Hall<sup>74</sup> feel that brucella encephalomeningitis may easily be missed by the clinician and should probably be considered in the etiology of any obscure chronic inflammation of the central nervous system. They cite 2 cases observed by them. One man had been ill for about 2 years, and had signs of involvement of the central nervous system, which had appeared about 4 months before admission to the hospital. Blood cultures were consistently sterile, but *Br. abortus* was cultured from the cerebrospinal fluid. Streptomycin sterilized the fluid, but was discontinued on account of drug fever and rash, treatment being continued with sulfadiazine. The patient left the hospital improved but still complaining of lightheadedness and diplopia. After his return home, he had weekly attacks of fever during the first 2 months, and was in poor health for at least 6 months. A year later he had an apparent recurrence of central nervous system involvement, with headaches, tinnitus, fever and chills. Aurcomycin was given in 2 courses and the patient has been well for 6 months.

The second case was that of a seventeen-year-old boy who had suffered from brucellosis for about 4 years. In the latter part of 1946, following a head injury, he became delirious, and experienced a fever of 104°F. Penicillin and sulfadiazine controlled the

manifestations, but after his discharge from the hospital he continued to suffer from lack of appetite, vomiting and fatigue. Nearly a year later, sulfadiazine treatment was stopped and shortly after he became delirious and feverish. Blood cultures were sterile, but *Br. abortus* was recovered from the cerebrospinal fluid. Penicillin and sulfadiazine were again given with satisfactory effect, but the patient continued to have episodes of fever, nausea and vomiting, and complete nerve deafness developed. Streptomycin and sulfadiazine were given in combination, but apparently without much benefit. About 2 months before admission to the hospital he had a recurrence, at which time the organism was again found in the cerebrospinal fluid, nearly 2 years after the initial culture. Streptomycin and sulfadiazine were given at first but streptomycin was soon replaced by the oral administration of 1 Gm. of aureomycin daily for 4 days, then 0.5 Gm. daily for 3 weeks. The patient did well and recovered his appetite. He left the hospital mentally and neurologically normal, except for some minor findings suggesting diffuse involvement of the nervous system and particularly of the spinal cord. The CSF remained sterile. Six months after aureomycin treatment, the patient was in good health and cultures of blood and CSF remained sterile.

Piéri, Panzani, and Guigou<sup>57</sup> have obtained cure with aureomycin in 1 case of acute *Br. abortus* encephalitis. Knight and associates<sup>37,38</sup> observed remarkable improvement, without subsequent recurrence, in a woman who developed *Br. melitensis* bacteremia and meningoencephalitis, shortly after bearing an apparently normal child. On aureomycin therapy, she was afebrile in 72 hours.

Westermann<sup>77</sup> has reported the cure by means of aureomycin of 2 cases of *Br. abortus* encephalitis and psychosis. One of the patients was critically ill with a miliary form of the disease and showed not only encephalomyelitis but also endocarditis and the hepatolienal syndrome (liver involvement with congestive splenomegaly). To this patient, streptomycin and a barbiturate were first given, but had little effect. With aureomycin, both patients were

afebrile inside of 5 days and signs of infection disappeared rapidly, although the severe anxiety state had not completely vanished 3 months later.

Puig and Bertrand<sup>60</sup> report the case of a forty-six-year-old man with brucellosis, complicated by labyrinthar sclerosis, psychic disturbances, delirium and meningeal reaction. Thirty-nine Gm. of aureomycin were given in all, with restoration of normal temperature in 4 days, and complete cure. They gave aureomycin to another patient with brucellosis complicated by meningoencephalitis. The patient was in coma at the time of admission and had convulsions, and urinary and fecal incontinence. Treatment with streptomycin had no effect. Aureomycin, 45 Gm. in all, produced normal temperatures in 9 days, and there was no relapse.

Benhamou and his associates<sup>8,9</sup> reported a number of cases of grave encephalitis and myocarditis, in the course of typhoid fever, which were cured by combined therapy with aureomycin and chloramphenicol. One child showed no response to chloramphenicol until aureomycin was given.

Debray and co-workers<sup>15</sup> observed a case of paratyphoid *b*, with myocarditis and encephalitis, in which the addition of aureomycin to the chloramphenicol which was being used in treatment seemed to have a definitely favorable influence on the evolution of the encephalitis. During 3 days of chloramphenicol treatment, cardiac and nervous signs and symptoms became accentuated. On the third day, definite signs of psychomotor encephalitis appeared, with complete disorientation as to space and time. There was rapid tremor of all the limbs, hypertonia and "cogwheel" sign in the upper limbs, exaggeration of postural reflexes, and catatonia. On the day after beginning aureomycin, the fever had dropped, the tremors appeared only during motion, and the hypertonia had disappeared. The patient returned to consciousness and her cardiovascular condition improved. The authors feel that this extremely grave case of paratyphoid would have been fatal without the use of both antibiotics. Since antibiotic therapy may tend to interfere

with the development of active immunity, the authors recommend vaccine (TAB) therapy in progressively increasing doses, in an attempt to diminish the frequency of relapses and complications. In 3 cases reported by them, including the above case of encephalitis, vaccination was begun 4 or 5 days after return to normal temperature and given in 3 injections at 6 or 7 days' interval. A satisfactory rise in the agglutination titer against eberthellae and against paratyphoid bacilli was observed.

Brault and Lévêque<sup>11</sup> gave aureomycin to 12 infants with influenzal (viral) encephalitis, 10 of whom recovered; and to 1 child suffering from vaccinal encephalitis, who was deeply comatose and catatonic. In this patient, there was complete transformation of the clinical picture in 48 hours and recovery in 8 days. Seven of the influenzal cases also received penicillin. The authors note that in the various cases of influenzal encephalitis with which they have had to deal, aureomycin has brought about clearing of the neurotoxic state within 12 hours; disappearance of the diarrhea within the same period; rapid return to a normal state of water balance; and finally complete cure without complications.

In a case of severe influenza virus encephalitis in a five-year-old child, Huber and associates<sup>32</sup> administered aureomycin by nasal tube, fluids rectally, digitaline, epinephrine and prostigmine. For 3 days, there was little change, but on the fourth day, spectacular improvement began and continued without interruption to complete cure. The child was regarded as convalescent on the sixth day of treatment.

Rashid<sup>61</sup> has reported the case of a year-old child suffering from severe dysphagia, and admitted to the hospital as an emergency. She was unable to swallow and there appeared to be paralysis of the constrictors of the pharynx. The child had suffered from fever of 100° to 104° for the past month, but had become afebrile 2 days before the onset of dysphagia. Neurological examination suggested encephalitis. The temperature on the day of admission was 103°F. with pulse 140 and respirations 40. Injections of vitamin B

complex and penicillin were given for 3 days without much benefit. While the temperature came down to and remained at 98.6°, pulse and respiration were still elevated. On the fourth day, treatment was begun with aureomycin, given in solution through a stomach tube (1 capsule initially— $\frac{1}{4}$  capsule every 4 hours for 8 days). Rapid improvement followed. Some return of the ability to swallow returned on the seventh day and recovery was complete on the eleventh day.

## Meningitis

The cerebrospinal fluid is almost defenseless against infection and once the invading organism has reached the subarachnoid space, rapid spread follows. Before the development of modern chemotherapy, the prognosis of cases of purulent meningitis, caused by organisms other than the meningococcus, was very poor.<sup>75</sup>

Present-day drugs have greatly improved the over-all prognosis for all forms of meningitis.<sup>36</sup> Orally administered aureomycin enters the spinal fluid, reaching a concentration approximately half that of the serum<sup>27</sup> and has brought about recovery in a number of cases of meningitis due to susceptible organisms, including *Staph. albus* and *aureus*, *Strep. faecalis*, *pneumococcus*, *A. aerogenes*, *Ps. aeruginosa*, and *H. influenzae*; as well as in some cases presumed to be of virus origin.<sup>3,6,13,18,19,31,48,54,55,69,76</sup>

Oral aureomycin has been found by Whitlock and co-workers<sup>78</sup> to pass into the spinal fluid of children who are not suffering from meningitis, and they conclude that intrathecal administration should be unnecessary in the treatment of meningeal infection with this antibiotic. The dangers of secondary infection, convulsive seizures, or inflammatory adhesions are ever-present when intrathecal injections are made.<sup>54</sup> The use of aureomycin intrathecally is not recommended.

In critically ill patients, prompt treatment is essential, and should be started without waiting for the result of sensitivity

studies. The very wide antimicrobial range of aureomycin suggests that it is an excellent choice for such initial therapy in all cases.

In France, the value of aureomycin in the treatment of infection occurring in newborn infants, including meningitis and encephalitis, has long been recognized.<sup>11,12,63</sup> In one series of 13 cases of brain or meningeal infection reported by Brault and Lévêque,<sup>11</sup> there were only 2 deaths.

*Bacterial Meningitis*—Aureomycin, as previously noted, is active against all of the common bacterial invaders of the meninges, as well as against some of the rarer ones. Its action begins within a very few hours after oral administration, while in gravely ill patients or in those who are unable to take medication by mouth, intravenous aureomycin begins to produce its effects very quickly.

Neter and his colleagues<sup>54</sup> reported cure with aureomycin of acute purulent meningitis in 2 children in whom infection and fistula formation had developed following operation on the spinal cord. In 1 case caused by *Ps. aeruginosa*, the antibiotic was given orally, rectally and intravenously; and in the other case, where the infecting organism was *A. aerogenes*, it was given intrathecally, as well as by the above routes, when infection persisted in spite of therapy.

A number of workers<sup>3,55,69,72</sup> have observed satisfactory bacteriologic response in staphylococcal meningitis. Forman<sup>25</sup> presented the case of a fifteen-year-old boy with infection of the left frontal sinus following injury to the head 2 years previously, and complicated by *S. aureus* meningitis. Control of the meningitis by aureomycin permitted operation on the sinus and complete recovery.

Rosenthal and co-workers<sup>66</sup> have described the case of a ten-month-old child in whom, after a tuberculous meningitis had been controlled by streptomycin, there developed a secondary *Strep. faecalis* meningitis. Administration of a sulfonamide, penicillin and streptomycin failed to produce sustained response and *in vitro* studies showed the organism to be resistant to large amounts

of both antibiotics. Marked improvement took place when aureomycin and penicillin were given, but was not sustained. Relapse occurred, and was controlled by the use of aureomycin alone. The authors felt that use of penicillin and aureomycin together was less effective than that of aureomycin by itself.

Kerr and Shaw,<sup>36</sup> however, believe that in either streptococcal or staphylococcal meningitis, therapy should be massive and multiple, and suggest that a satisfactory combination might be aureomycin, sulfadiazine and penicillin, in large doses.

In *H. influenzae* meningitis, aureomycin appears to be more effective than sulfadiazine or streptomycin. Severe cases, particularly in infants, should probably receive sulfadiazine as well.<sup>13</sup> In very severe cases, aureomycin may be given in combination with streptomycin, sulfadiazine, and antiserum.<sup>72</sup> If streptomycin is discontinued by the fifth day, it is presently believed that there is very little chance of eighth nerve injury.<sup>36</sup> Fifteen cases, successfully treated with aureomycin, have already been reported.<sup>13,20,23,72,76</sup>

In a child with *H. influenzae* meningitis, treated by Alderman,<sup>2</sup> the infection failed to respond to intramuscular and intrathecal streptomycin plus sulfadiazine. Aureomycin was administered with rapid favorable response.

It is apparent that the combination of pyarthrosis and meningitis as complications of *H. influenzae* infection indicates a very severe infection. None of the previously reported cases of this condition recovered. Joslin and Howard<sup>34</sup> report survival of 1 case treated with aureomycin. Residual brain damage resulted but the patient, at the time of reporting the case, was still showing improvement. The end result was, of course, still uncertain.

The entrance of *E. coli* into the blood stream and the development of a general infection is not so rare an occurrence as has been thought, and may follow infection of various organs such as the urinary system, gall bladder or bowel. Following systemic invasion, the organism may localize in soft tissue, pleura, endocardium or meninges. Although some success has been attained with strep-

tomyacin in the treatment of *E. coli* meningitis, aureomycin appears to give better results.<sup>36</sup>

Acker<sup>1</sup> has reported the case of a six-week-old boy with *E. coli* meningitis, which became evident on the fifth day of a gastroenteritis. On the seventh day, there was a rise in temperature and greenish yellow coloration of the skin, which the author considers typical of coli sepsis. The child's condition rapidly deteriorated and within 24 hours he evidenced signs of meningitis. The spinal fluid culture showed *E. coli*. Streptomycin was given both intramuscularly and intrathecally with response in 24 hours, although *E. coli* was still present in the CSF. Relapse occurred on the fourth day of streptomycin treatment and increased dosage was unable to control it. The organisms multiplied in the spinal fluid and had obviously become resistant to streptomycin. Aureomycin was therefore substituted, in the usual dosage of 25 mg. per kilo per day, given orally through a tube. In 36 hours the child was obviously better, free of fever, and had a decreased cell count in the spinal fluid. The organism was, however, still present in the fluid. On the eighth day the temperature rose again, and the dosage of aureomycin was raised to 40 mg. per kilo. Twelve days later the meningitis was cured. This case illustrates the obvious necessity for individualization of dosage in serious cases of this kind.

Laurell and associates<sup>43</sup> have reported the successful treatment of *E. coli* meningitis in a premature infant who, prior to his illness, had severe scleredema which subsided when treated with vitamin E. A day after this condition cleared, the child showed fever which persisted for 10 days off and on, at the end of which time signs of meningitis developed, although penicillin was being given prophylactically. The child was given treatment with streptomycin, a sulfonamide, and heparin. The coliform bacilli in the fluid were found to be extremely sensitive to aureomycin, which was then substituted for other forms of treatment, on the eleventh day of life. The daily dose was 70 mg. per kilo of body weight for the first 3 days, and was then reduced to 35 mg. per kg. Vitamin B was



given concurrently. Three days later, the temperature was normal and the infant began to gain weight. On the second day of treatment, the spinal fluid was sterile and the infant's general condition was quite satisfactory. At the age of 4 months, the child was apparently normal, mentally and physically.

Poulton<sup>58</sup> reports cure of *E. coli* meningitis in a baby of 6 weeks, following treatment with streptomycin both intraventricularly and intramuscularly for 5 days, and sulfadiazine and aureomycin orally for 14 days. Two injections of streptokinase were made into the ventricles. The baby responded immediately to this treatment and was discharged after 3 weeks in hospital. Ten months later, his development appeared to be normal. Poulton suggests that a "dry tap" may be characteristic of *E. coli* meningitis. It should be noted that sensitivity tests on the organism in this case showed it to be less sensitive to streptomycin than to aureomycin.

A number of workers<sup>19,31,45,48</sup> have reported the successful treatment of pneumococcal meningitis with aureomycin.

Arnold<sup>5</sup> draws attention to the fact that recovery from an attack of purulent meningitis is no longer unusual and that the attention of the physician must now be devoted to the preservation of normal mental and physical status. The early recognition of such complications as purulent or serous subdural effusion is important. He reports a case of pneumococcal meningitis in a three-and-a-half-month-old boy, which responded to aureomycin, except that the child continued to have low-grade fever and stiffness of the extremities. Subdural fluid could be demonstrated bilaterally, and repeated subdural taps brought about great improvement. Some retardation in development was observed at the time of the child's discharge from hospital; but 6 weeks later, he was healthy and showed normal behavior for his age.

Reinhart<sup>62</sup> has reported a case of pneumococcus type 6 meningitis in an infant, which responded to aureomycin, given as soon as the etiology had been determined. No response had occurred

to a sulfonamide, streptomycin and penicillin. The child recovered but, 4 weeks after admission, showed spasticity and some apparent loss of vision.

In a group of 54 patients with pneumococcal meningitis, treated by Lepper and Dowling either with penicillin, or with penicillin plus aureomycin,<sup>44</sup> there were clear indications that aureomycin, given at the same time as penicillin, interfered with the action of the latter against the organism. The authors concluded that it is unwise to use a combination of penicillin with either aureomycin, terramycin or chloramphenicol.

Hain<sup>30</sup> states that in acute febrile illness there is a decrease in the eosinophil count, as a reaction to stress, and that this decrease seems to reflect the adequacy of the adrenocortical reserve. She suggests that this finding may be used as a measure of the prognosis, failure to drop to zero or thereabouts during acute, severe stress, indicating poor adrenal response; and notes that in 1907, Lams<sup>41</sup> called the eosinophil count an "index of convalescence." Hain refers to one case of pneumococcal meningitis, in which the eosinophil count at the onset was zero, and in which striking clinical recovery followed the administration of penicillin and aureomycin.

*Klebsiella pneumoniae* has been found in less than 0.5% of all cases of meningitis. In 50 years, fewer than 100 cases have been reported, and there have been very few recoveries.

During the pre-sulfonamide period, the death rate in cases of Friedländer meningitis was well over 90 per cent, and residual effects were common. Treatment with sulfonamides reduced the mortality to approximately 50 per cent. This rate was somewhat decreased by the use of combined treatment with penicillin and sulfonamides, being reduced to about 38 per cent. The rarity of this type of meningitis does not permit any accurate estimate of its mortality following the use of streptomycin and the other broad-spectrum antibiotics, but the few case reports published in the last half-dozen years indicate that the results are better than with the sulfonamides, with or without penicillin.

In a review of Friedländer meningitis by Bombardier,<sup>10</sup> the author calls attention to the fact that in most cases there exists also extrameningeal localization and such local infection seems often to precede the development of meningitis. He therefore believes that primary Friedländer meningitis is very rare, and that it is usually the result of direct extension from a near-by infectious focus, or from the oropharynx or the intestine; or of a bacteremia proceeding from such localized infection. This observation is of primary importance, because the suppression of these extra-meningeal infections is indispensable if cure is to be obtained and relapse prevented. The localized infection may take the form of an otitis, a sinusitis, sore throat, pneumonic infection, cholecystitis, urinary infection, skin ulceration. General infection may also result from the presence of the Friedländer bacillus as a saprophyte in the digestive tract. In infants, toxicosis, convulsions, somnolence and torpor are of frequent occurrence, and there is often interference with the circulation of the spinal fluid. The course of the disease is slower than in the adult, lasting usually about twice as long.

Evans and associates<sup>23</sup> have treated 4 cases of Friedländer's bacillus meningitis. Three given sulfonamides died and 1 given aureomycin recovered. Three of the 4 cases, including the 1 treated with aureomycin, were diabetics. The successfully treated patient had a history of otitis media since early childhood and of diabetes first diagnosed 6 years previously. Penicillin and sulfadiazine were administered as soon as he was admitted, pending the results of *in vitro* sensitivity tests on the cultures from the spinal fluid and ear. Of the 5 antibiotics tested, aureomycin was much the most effective. In decreasing order of activity came streptomycin, terramycin, chloramphenicol and penicillin. Combined oral and intravenous aureomycin was maintained for 10 days, and medication was then continued orally. The clinical status improved remarkably, but pus continued to drain from the left ear and culture revealed *Klebsiella pneumoniae* type A. The chronic nature of the ear infection made it impossible to attack the otitis systemically,

and since no change in bacterial sensitivities could be detected, aureomycin solution was instilled locally. Drainage stopped on the second day. Treatment was continued for 15 days, and there has since been no drainage. A few days after the left ear dried up, signs of purulent otitis developed in the right ear. Aureomycin was again found to be the best agent, and local treatment to the right ear for 17 days cleared this condition also, the discharge ceasing on the second day. The patient was discharged in good health after a hospital stay of 6 weeks. Keefer<sup>35</sup> considers that streptomycin and aureomycin are the drugs of choice in all Friedländer infections.

Martin and co-workers<sup>50,51</sup> have reported 2 cases of purulent meningitis, produced by the Gram-negative bacillus *Moraxella lwoffii*, an extremely rare invader of the central nervous system, though often seen in eye infections. Both proved fatal by reason of the profound cachexia of the patient, although the spinal fluid became sterile in each case. In one of them a striking response to aureomycin was observed. Seventeen days after the removal of a meningioma of the left posterior fossa, meningeal signs developed and rapidly became severe. In spite of intensive treatment with penicillin, streptomycin, and sulfonamides, coma deepened; the patient was unable to retain anything, and finally became completely unable to swallow. Study of bacterial sensitivity showed high resistance of the bacillus to penicillin and to streptomycin, but extreme sensitivity to aureomycin. Aureomycin being at that time commercially unavailable, the authors pursued the former treatment, together with blood transfusions, for another 20 days, while the patient gradually became worse. Twenty-nine days after the beginning of the illness, the authors were able to obtain some aureomycin, but were almost hesitant to give it to the patient, such was her profound cachexia and desperate condition. On the day after beginning aureomycin, the spinal fluid was less purulent and the bacterial colonies less numerous on culture. Forty-eight hours after beginning aureomycin, the spinal fluid was sterile. However, the patient's condition deteriorated still further, and cachexia was

the eventual cause of her death. Autopsy showed that the site of the meningioma was filled with a sterile purulent liquid. There was no abscess or focus of infection, and no spinal block.

Salmonella meningitis is of rare occurrence, and is highly fatal, particularly in infants, the recovery rate before the sulfonamides being 2 per cent in patients less than 9 months of age and about 20 per cent in older children. Padnos and Goldin<sup>56</sup> have described a case due to *S. bareilly*, in a four-year-old girl. Treatment was begun with penicillin and dihydrostreptomycin intramuscularly, aureomycin and sulfadiazine intravenously, but on identification of the organism and tests of its sensitivity, other medication was discontinued and aureomycin continued intravenously, 100 mg. every 4 hours. The patient responded well and was discharged completely cured on the twenty-second hospital day.

*Listeria monocytogenes* is also a rare cause of meningeal infection. A few cases have recovered under treatment with penicillin and sulfadiazine, or with penicillin, sulfadiazine and streptomycin. Line and Cherry<sup>46</sup> report 2 cases, both in young infants. One case, treated with penicillin, sulfadiazine, and dihydrostreptomycin proved fatal; but in the other, partial recovery followed the use of aureomycin. The child had shown no response to penicillin, chloramphenicol, and dihydrostreptomycin, even in large dosage. Sensitivity determinations showed the organism to be very much more sensitive to aureomycin than to any of the antibiotics being used. The child regained apparently normal health and growth was unusually rapid. The only apparent residua were a slight downward deviation of the right eye and an occasional fine vertical nystagmus. Some months later obstructive hydrocephalus developed, for which operation was performed. The child had a fatal postoperative pulmonary complication, and died 8 months after her recovery from the meningitis.

While chloramphenicol is generally conceded to be the remedy of choice for typhoid infection, Ripy<sup>64</sup> has reported a case of typhoid meningitis in a thirteen-month-old child, cured promptly

by aureomycin, after failure to respond to chloramphenicol.

If, following the rupture of the membranes, the amniotic fluid becomes contaminated by the vaginal flora, infection of the fetus may result, through swallowing or aspiration. Generally such infection takes the form of bronchopneumonia, but it may produce meningeal involvement or, if intracranial hemorrhage has occurred, may invade the blood clot. Antibiotics and sulfonamides, effective as prophylactic agents, are often of little value in the cure of established infection. Clavero Nuñez<sup>14</sup> has used aureomycin in 4 cases of infected intracranial hemorrhage. The infants improved temporarily after lumbar puncture, but then began to lose weight. Penicillin and sulfonamide therapy were ineffective, but aureomycin brought about rapid recovery, in a dosage of 250 mg. daily, given in small doses at each feeding. The average duration of treatment was 4 days, and in no case was it more than 1 week.

*Viral Meningitis*—Grater and Rider<sup>29</sup> reported on the treatment of 2 cases of lymphocytic choriomeningitis, in both of which oral aureomycin produced marked relief of symptoms, with considerable decrease in meningeal signs, within 24 hours. Within 96 hours, the patients were afebrile and clinically well. One month later the spinal fluid proteins and lymphocytes, while showing marked decrease, were still above normal levels.

Brault and Lévêque<sup>11</sup> have reported the use of aureomycin in 2 children, suffering from an "aseptic" meningitis, apparently of virus origin. Aureomycin brought about cure in these children after other antibiotics had failed.

One case of adult mumps, reported by Spinelli, Cressy and Kunkel,<sup>73</sup> showed evidence of lymphocytic meningitis, with confusion, listlessness and headache. The Kernig and Brudzinski signs were absent but there was mild nuchal rigidity. On admission, the patient's temperature was 102°, but there was no evidence of parotid or testicular swelling or tenderness. On the fourth hospital day, the temperature rose to 104°F. and a day later the right testis became inflamed. In view of the high temperature and the presence

of complications, aureomycin was given. Normal temperatures were reached in 16 hours and, inside of 24 hours, the inflammation of the testis had subsided and the patient was free of symptoms. During his hospital stay, mumps-complement fixation studies showed a rising titer.

## *Infections of the Peripheral Nervous System*

*Herpes Zoster*—Aparicio<sup>4</sup> has described the development of herpes zoster of the thorax during the course of Malta fever. Aureomycin was given for the original infection, and the author was interested to observe that the herpetic lesions were rapidly disappearing at the end of 24 hours. The patient recovered rapidly. Two months later, there was no evidence of relapse of either brucellosis or herpes.

Lacroix<sup>40</sup> noted good response to aureomycin treatment in herpes zoster in a man of 61. Pruritus sharply diminished, 19 hours after beginning aureomycin. Forty-six hours after the beginning of treatment, pain and pruritus had vanished and the vesicles were disappearing.

While most frequently observed on the trunk, herpes zoster may involve the head and extremities. Sacino<sup>67</sup> has observed 1 case in which the arm and adjacent chest were involved; Jepsen,<sup>33</sup> 1 in which the tongue was the site of herpes; and Shedrow,<sup>70</sup> 3 cases of herpes of the lower extremities, one of them coincident with varicella. Aureomycin was used with very good effect in the first 2 cases and in the herpes-varicella case.

While ophthalmic involvement by the virus of herpes zoster is infrequent, a number of recent reports have testified to the value of aureomycin in this condition. In former days, there was no effective remedy for the viral infection or for alleviation of the intense pain. Involvement of the ocular muscles and permanent corneal damage are to be feared.

Rosenberg<sup>65</sup> has reported 2 cases of ophthalmic zoster in one of which the eyeball was involved. Complete healing followed

the use of aureomycin, and there were no ocular complications or residues. Pritikin and Duchon<sup>59</sup> have also reported a case successfully treated with aureomycin.

Benedek<sup>7</sup> observed most gratifying results from aureomycin treatment in a severe case of herpes zoster, extending over the entire right side of the face onto the scalp, and including the right eye. Many of the zoster vesicles became necrotic, and the pain was excruciating. Within 24 hours after beginning aureomycin, the frontal redness was fading, the edema was reduced and the scabs were falling off. Fever had disappeared, pain had diminished, and the patient was able to open her right eye slightly. After 72 hours (3 Gm. aureomycin), edema was very much less and the vesicles were clearing. Pain was only slight, the eye could be half opened and the patient was in general much improved. Two weeks after admission there was complete healing of all the lesions. For some time after discharge, the patient suffered from severe pain in the trigeminal distribution, but this had almost disappeared when she was seen 6 weeks after the end of treatment. The author points out that 1 Gm. daily was found to be fully adequate and was the same dosage as that used by Rosenberg.

Delorme and Rouher<sup>16</sup> have treated 32 cases of corneal herpes with aureomycin instillations. The cases were not discussed in detail, but certain conclusions were drawn by the authors as to the rational treatment of this condition. They began by treating a few cases of dendritic ulcers of the cornea by oral administration of 1 or 2 Gm. of aureomycin daily, but saw no evident response, a result which they do not consider surprising in view of the fact that de Roeth<sup>17</sup> was unable to find aureomycin in the aqueous or in the cornea when it was given by mouth. They then turned to the use of local instillation, but at first were unable to obtain the ophthalmic solution and made up their own from aureomycin capsules. Although these instillations were irritating and painful, they were bearable and were of great value to the patients. Later they used the ophthalmic solution of aureomycin borate and found



it to be tolerated perfectly, when 1 or 2 drops were given every 2 hours, day and night. Among the 32 patients there were 12 spectacular cures, complete in 2 to 6 days; 10 of these cases were of recent development and involved only the epithelium, without infiltrating the corneal stroma. In the 20 remaining cases, many of them chronic and resistant to various other medications, success was less prompt and spectacular. In these serious cases, local treatment alone relieved, without curing, the superficial lesions, but it had not, in 5 or 6 days of treatment, had any effect on the lesions of the stroma. Firm, meticulous brushing of the cornea with dry cotton wool favored the action and the penetration into the cornea of the aureomycin drops and appeared to shorten the period of evolution, so that arrest of the infection took place early.

A case of herpes zoster ophthalmitis, reported by Shier and Provisor,<sup>71</sup> gave a history of head pain for 5 days and frontal eruption for 3. Routine therapy was given for 1 day, following which the patient was lethargic, and the eyelids swollen shut. On the third day, he had a temperature of 102.5°F., was confined to bed, slept almost all the time and was irrational. Twenty-four hours after beginning aureomycin orally, the patient was strikingly improved and the temperature had started to drop. In 72 hours, the temperature was normal and the lesions gradually and progressively disappeared.

Fabregoule and Larmande<sup>24</sup> observed a case of ophthalmic herpes zoster in which pain preceded vesiculation by 4 days. The eruption involved the left nasal and frontal region and there was a small corneal ulceration. Although aureomycin had little effect on the pain, and although the fever abated only after several days, the corneal ulceration was cured in 48 hours. In spite of the significant and fairly rapid response to treatment, certain residual lesions remained, including corneal hypoaesthesia and oculomotor paralysis. Thus while aureomycin is undoubtedly of great value in most cases of herpes zoster, it is not the complete answer to the therapy of ophthalmic involvement.

Lanfranco<sup>42</sup> has reported prompt response to aureomycin, and cure in 6 weeks, in a case of ophthalmic herpes zoster with facial edema, great swelling of the eyelids and corneal ulceration. Pain was not a feature during or after the illness.

Goodson<sup>28</sup> gave aureomycin to an extremely severe case with beginning signs of iridocyclitis and prostrating pain. The patient's general condition was extremely serious, and the whole of the affected area was involved in a confluent pustular eruption which by its severity suggested smallpox. Twelve hours after the first dose of aureomycin, the patient's condition changed dramatically for the better; and at the end of 24 hours, the eye was completely clear, only a few clean dry crusts remaining of the eruption. The entire attack lasted a little over 7 days. Goodson remarks that she has never known any other remedy comparable to aureomycin in effectiveness against this infection.

Encephalitis is an extremely rare complication of herpes zoster, and the only 4 proven cases reported in the literature have all died. Foster and Jackson<sup>26</sup> have observed 1 case in which encephalitis developed during the second week of a severe extensive herpes zoster of one lower limb and the lower abdomen. The patient suddenly became feverish and disoriented and was admitted to hospital. There were scattered vesicular lesions over the thorax, neck and face. Twenty-four hours later, his mental condition had become aggravated and retention of urine developed. Aureomycin was started that afternoon (0.5 Gm. every 4 hours) and definite improvement could be seen by the following morning, the patient having become almost completely rational. He was discharged 5 weeks after admission, the chief observable abnormalities being an irregular, rapid pulse and a small ulcerated area on the thigh. The authors point out that this is both the first recorded incidence of the use of aureomycin in herpes zoster encephalitis and the first published case of survival following this infection.

*Neuritis*—Although the present-day tendency is to attribute all cases of sciatica to a vertebral lesion, that this is not universally

true becomes obvious when one considers the number of cases of sciatica which occur in the course of an infectious condition, such as sore throat, intestinal infection, or influenza. Monnerot-Dumaine<sup>52,53</sup> has reported a case of sciatica whose infectious origin was proved by its remarkable response to aureomycin. The patient had suffered from sciatica for several months; there had never been lumbago. The beginning of the illness dated from 5 days after exposure of the lower limbs to cold. The intensity of the sciatica was for a long time only moderate but it did not respond to various treatments, including vitamin B<sub>1</sub>.

An application of radiotherapy produced within 36 hours a painful febrile exacerbation, requiring morphine. The fever persisted, rising toward nightfall with increase of pain. Opiates procured some sleep for the patient but scarcely touched the pain. The only points suggesting a possible focus of infection were a raised sedimentation rate, a history of salpingitis which was said to have been cured by surgery, and mild chronic colitis with constipation. The sedimentation rate was 45 to 75. The author prescribed aureomycin, intradermal histamine on the posterior surface of the thigh and a neurotropic vaccine (neuro-gatren). He states that the effect of aureomycin was immediate and spectacular. From the very first night analgesics could be cut in half, and were stopped after the second night. The intensity of the pain diminished rapidly, until at the end of 36 hours, there was only slight intermittent discomfort. Both the sedimentation rate and the temperature dropped. A few days later the patient got up and went out to celebrate the Christmas and New Year holidays, and had a relapse which responded in the same spectacular manner to aureomycin. Improvement was observed within 5 or 6 hours, and pain had almost completely disappeared 36 hours later. However, in view of the previous relapse, the author gave a longer course of treatment than before, the patient receiving 12 Gm. of aureomycin in all.

The results obtained in the above case encouraged Monnerot-Dumaine to continue the use of aureomycin in other neuritides.

He obtained considerable improvement in 2 or 3 days, in another case of sciatica of nonvertebral origin and 1 of cervicobrachial neuralgia.

Eulogio Vasquez<sup>22</sup> studied 2 cases of involvement of the optic nerve in the course of a meningoencephalitis, which was probably of virus origin; one an optic neuritis of the descending type, the other a papilledema. Both the brain involvement and the optic nerve disease yielded rapidly to aureomycin treatment, normal conditions being found on subsequent functional, physical, and ophthalmoscopic examination.

## CHAPTER FIVE

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## INFECTIONS PRIMARILY INVOLVING THE CARDIOVASCULAR AND LYMPHATIC SYSTEMS

**I**NFECTION of the systemic circulation usually indicates infection elsewhere in the body. It is a disabling and painful condition and tends to interfere with nutrition, oxygenation and elimination of waste in the tissues supplied by the affected vessel. Obstruction of the vessel lumen results in edema and embolism, ischemia and necrosis, or lymphedema, according as the involvement resides in vein, artery or lymphatic.

Prevention of vascular infection is important and requires prompt therapy of infectious foci, by surgery if necessary, and avoidance of circulatory stasis. Modern systemic chemotherapy is a powerful prophylactic weapon, and is also of great value in the treatment of established vascular infection. Cobb<sup>17</sup> states that lateral sinus thrombosis, once a frequent complication of aural and nasal infection, is now rare.

Once inflammation of a vessel in the extremities, or a superficial vessel, has developed, certain fundamental points must be observed: elevation of the affected part; rest, avoidance of deep breathing, coughing or straining; application of hot wet dressings along the full length of the involved limb, to relax the vessel walls; administration of vitamin C,<sup>48</sup> and use of an elastic stocking. The tendency to thrombosis is increased by dehydration. Increased salt intake is contraindicated. Aureomycin has been found a valuable aid to treatment.

Many favorable reports have been published on the use of aureomycin in infection of the cardiovascular system, infection which, even if nonfatal, is often associated with prolonged or permanent disability.

Broustet<sup>10</sup> points out that death in severe infectious disease often results from toxic myocarditis, and that control of the infectious state permits the restoration of normal cardiac function. This has been found to be true also in endocarditis lenta; in some cases, at the same time as the infectious and renal signs regress, edema disappears and the radiologic dimensions of the heart are notably decreased, as the vegetations and blood stream become sterilized. Broustet says that he has himself been lucky enough to observe 4 such cases, in which control of the endocarditis by antibiotics brought about improvement in the heart condition.

Nichols<sup>54</sup> recommends the prophylactic use of penicillin or aureomycin when operation on the heart or thorax is contemplated.

Aureomycin has been recommended for the prevention of sub-acute bacterial endocarditis in cardiac patients undergoing operations on the nose, the throat, gastrointestinal and genitourinary tracts.<sup>44,49,67</sup>

Rabinovici and Fine<sup>59</sup> have found that, in severe blood vessel injury, oral aureomycin will prevent gangrene and death of the tissues supplied by the affected vessels, provided that the injury involves either the venous or the arterial circulation, and not both. Aureomycin acts by inhibiting bacterial invaders which might cause further damage to the vessels and impede the development of collateral circulation. The authors found that in experimental damage to intestinal vessels, such as may occur in one-stage anastomosis, oral aureomycin promoted the re-establishment of adequate circulation, permitting return of bowel function and recovery in nearly all cases. The degree of vascular injury which they inflicted was sufficient to produce gangrene and death (in 40 hours) when aureomycin was not used.

Seybold and Musgrove<sup>69</sup> recommend the prophylactic use of



aureomycin when continuous gastrointestinal suction is used in the treatment of mesenteric vascular occlusion, and its continuation for several days after removal of the tube. Heparin, they believe, should be begun as soon as operation is completed.

## *Arteritis*

The 2 conditions most frequently considered under the heading "arteritis" are periarteritis nodosa and thromboangiitis obliterans, both of unknown origin. An infectious factor, though suspected by some workers, has not been demonstrated.

It seems likely that periarteritis represents a hypersensitivity reaction to a number of nonspecific agents, including substances of parasitic, bacterial, vegetable and chemical origin (iodine, poison oak, horse serum, neoarsphenamine, tubercle bacilli, streptococci). Experimentally, the condition has been produced by exposure to cold or by the administration of desoxycorticosterone. Arterial lesions in trichinosis have been found to resemble periarteritis nodosa.<sup>52</sup> Some improvement followed the use of aureomycin in 1 case of polyarteritis nodosa (cutaneous form) reported by Slinger and Starck.<sup>70</sup>

The 2 conditions in which arterial inflammation is known, or believed, to be produced by an infectious agent are cranial (temporal) arteritis, and bacterial embolism from a cardiac vegetation in the course of endocarditis lenta. In the latter, if the organism responsible for the endocarditis is one of the many known to be susceptible to the action of aureomycin, it is to be expected that the arterial infection will heal as the heart infection clears.

Wright<sup>79</sup> describes cranial arteritis as a self-limited disease accompanied by fever, and always involving the temporal arteries. Other cranial arteries may also become infected. The disease may produce severe pain during many months, and the usual analgesics are often ineffective. The etiology is unknown, but is thought to be infectious; and there is usually a recent history of acute infec-

tious disease.<sup>62</sup> Oral infection, either accompanying or preceding the arteritis, is very common. Wright<sup>79</sup> advocates excision of the involved arterial segment for relief of severe pain.

Roberts and Askey<sup>62</sup> report striking relief of pain from injections of procaine hydrochloride (1 or 2 cc.) into the tissues surrounding the arteries. In most of these cases, the temporal artery was chiefly involved, but in 1 case in which the intracerebral arteries were apparently also affected, satisfactory results were obtained by stellate block. Disappearance of pain was immediate and was accompanied by softening and relaxation of the involved vessels.

Remarkable improvement following aureomycin was reported by Rice-Oxley and Cooke<sup>61</sup> in 2 patients with temporal arteritis lasting a month or more. Fever disappeared within 24 hours and both patients felt distinctly better. One patient exhibited intolerance to the drug; it was discontinued, and severe relapse occurred within 48 hours. The other patient improved steadily, and appeared to have completely recovered in 2 weeks.

Boquien and associates<sup>7</sup> have observed the very favorable action of aureomycin in a case of temporal arteritis with blood cultures positive for streptococci. The patient was a man of 78, whose eyesight had gradually failed during the previous few years, and who had suffered from fever and frontal headache for a month. The left lateral decubitus sharply increased his pain. Five days after admission, vision in the left eye was completely lost overnight. Examination showed marked papilledema in this eye, and thrombosis of the superior central vein. Resection of the left superficial temporal artery, which was found to be thrombosed and sclerotic, with chronic inflammatory lesions in all coats, was followed by marked relief of pain. Chills and fever persisted, and there was no return of visual acuity in the left eye. Repeated blood cultures were done, and on one occasion a streptococcus was isolated which was resistant to penicillin, to streptomycin and to sulfonamides. For this reason, and because of the paper by Rice-Oxley and Cooke,<sup>61</sup> the authors began the use of aureomycin. The patient

improved rapidly; strength and appetite returned, and he was able to sleep comfortably. Pain practically disappeared and painful paroxysms with chills were no longer observed. The left eye remained blind. The patient was discharged, very greatly improved, 16 days after aureomycin treatment was begun. The authors stress the gravity of temporal arteritis, in which the local disease is only the obvious expression of a very diffuse vascular process. Their patient had a fatal relapse several months after discharge.

Aureomycin cannot be expected to be uniformly helpful in temporal arteritis. Brown<sup>12</sup> has reported 1 case which was uninfluenced by sulfonamides, penicillin or aureomycin.

### *Endocarditis*

Before the introduction of sulfonamide drugs, recovery from bacterial endocarditis took place in less than 3 per cent of patients. The antibiotic substances now available can rid the blood of the causative agent in 95 per cent or more of the cases, but the proportion of cure is far less. Delay in diagnosis permits the pathogen to produce mural thrombi and otherwise cause damage to the heart or, through embolism, to other vital organs. Many patients throw off their infection under treatment with an antibiotic, only to die of cardiac insufficiency.<sup>39,42,44</sup> Inadequate dosage and improper choice of therapeutic agent will contribute to failure.

The best hope for reducing the still high (about 30 per cent) death rate<sup>44</sup> from subacute bacterial endocarditis rests mainly on: (a) Very early diagnosis, if possible before the vegetations have become luxuriant; when this occurs, the bacteria entrenched in the growths are almost inaccessible to drugs, and further cardiac damage is likely to develop.<sup>37</sup> Unexplained fever for a week or more, in the presence of a cardiac murmur, or arteriovenous fistula, is enough for a tentative diagnosis.<sup>22,24,44</sup> (b) Prompt selection of the effective remedy, according to the pathogen present, and its immediate administration in full dosage.

Most of the organisms responsible for infections of the endocardium are highly susceptible to aureomycin,<sup>5,24,26,29,57,71,73,77,80</sup> and a number of cures have been reported, many of them in patients who had not been helped by other antibiotics.<sup>1,4,13,14,20,21,26,29,30,34,42,46,71,72</sup> Its prophylactic use is recommended for cardiac patients who require dental, surgical or urethral manipulations.<sup>31,49,66,67</sup> Lillehei and associates<sup>43</sup> have shown experimentally that cardiovascular stress (such as is imposed by incompetent heart valves) so greatly increases the susceptibility of endothelial tissues that endocarditis can be produced by the entry of a comparatively small number of bacteria into the blood stream.

Success of treatment of subacute bacterial endocarditis depends on several factors: the choice of the suitable antibiotic, the early initiation of treatment before clinical symptoms and signs have become marked, the age of the patient, the size of the dosage, and the blood levels of antibiotic attained.

Relief of toxemia by successful attack on the microorganisms will sometimes be followed by improvement of cardiac function,<sup>10</sup> but tragically often, when treatment is finally instituted, control of the infection comes too late to prevent cardiac decompensation and death.

Aureomycin seems to have much less tendency to permit the development of resistant strains of organisms than do penicillin and streptomycin. Levinson and co-workers<sup>41</sup> have reported 18 patients with staphylococcal endocarditis during a 3-year period. Of these, 12 died. Aureomycin was effective in 2 cases not responding to penicillin; but in a third case, the organism developed increasing resistance to aureomycin, as it had to penicillin. Sensitivity studies on 15 of the cases revealed that 10 of the strains of staphylococcus were resistant to penicillin.

Often, positive blood cultures may not be obtainable. This seems to be true in cases of enterococcal infection, and in certain cases of endocarditis with a history of typhus, or with laboratory evidence of past or present rickettsial infection. Endocarditis in this

latter group may be a cardiac form of Brill's disease. The "post-typhus" form of endocarditis is characterized by an absence of previous heart disease, aortic localization, severity of the myocardial and other visceral symptoms, and negative blood culture. Electrophoresis shows a high gamma globulin level. The infection is resistant to penicillin, but has responded to aureomycin.<sup>14,15,20</sup>

Cattan and associates<sup>15</sup> have reported the effectiveness of aureomycin in 2 cases of penicillin-resistant endocarditis with negative hemoculture. The intradermal reaction to rickettsial antigens was positive, as was the Giroud "sero-protection" test. One patient recovered completely; the other was very much improved, but died of cardiac insufficiency. The endocarditis was strongly suspected, though not proved, to be of typhus origin in both cases.

In a case of bacterial endocarditis caused by hemolytic *Staph. albus*, reported by Allen and Riecker,<sup>2</sup> the infection did not respond to penicillin, and the patient became severely sensitized to this antibiotic. Combined administration of streptomycin and sulfamerazine was also ineffective. The patient was given 4 Gm. of aureomycin daily for 4 days, became afebrile and nontoxic, and was allowed to go home on a maintenance dose of 2 Gm. daily. After 15 days of aureomycin, the patient noted some increase of dyspnea and some reddening of the extremities. Attributing this to the medication, he stopped taking aureomycin. Six days later he was re-admitted, toxic and decompensated, with a temperature of 103°. Resumption of aureomycin brought about temporary benefit, but he died about 3 weeks after re-admission. Necrotizing verrucous vegetations were found at autopsy, involving the aortic and tricuspid valves through the interventricular septum, and there were numerous pulmonary and myocardial infarcts. The survival time in this case (14 weeks) was an unusually long one for *Staph. albus* endocarditis.

Hughes<sup>33</sup> has reported 3 cases of subacute bacterial endocarditis, 1 of them staphylococcal, which were apparently cured by means of aureomycin. The patients were followed after treatment for

periods of 4 to 10 months. In 1 thirteen-year-old girl, previous treatment with penicillin and caronamide had produced remission, but she relapsed about 6 months after discharge from the hospital. Blood cultures demonstrated a coagulase-negative hemolytic *Staph. albus*, resistant to penicillin, fairly resistant to streptomycin, and very sensitive to aureomycin. Aureomycin was then prescribed. The patient was discharged, apparently cured, after 5 successive blood cultures had been sterile. Six blood cultures obtained during 2 months of convalescence were also sterile.

The second case was that of a sixty-nine-year-old woman, with no previous history of heart disease, in whom *Str. viridans* endocarditis had developed following an attack of pneumonia some months previously. Before admission, temporary improvement had been produced by a course of 15,000,000 units of penicillin and by a course of 8 Gm. of aureomycin. Both of these amounts proved inadequate. The organism showed marked resistance *in vitro* to penicillin and streptomycin and only slight sensitivity to aureomycin. An initial dose of 500 mg. of aureomycin was given, followed by 250 mg. every 8 hours. Temporary remission resulted, but febrile relapse occurred on the seventeenth day of treatment. The doses of aureomycin were then increased to 500 mg. every 6 hours and the temperature gradually returned permanently to normal. In this case, as in the preceding one, blood cultures remained sterile and the cardiac murmur practically disappeared.

Subacute endocarditis is a rare but grave complication of bacterial pneumonia. It is important that attention be paid to the heart in any case of pneumonia, so that should this complication arise, it may be adequately dealt with by massive antibiotic therapy.

In a sixteen-year-old girl with congenital heart disease and *Str. viridans* endocarditis, complicated by bilateral basal bronchopneumonia, rapid improvement followed administration of aureomycin. The organism had been found resistant *in vitro* to penicillin and somewhat resistant to streptomycin. After a little more than

2 weeks of treatment, the pneumonic involvement had almost completely cleared. Ligation of a patent ductus arteriosus was done, aureomycin was given postoperatively, 3 Gm. daily for 2 weeks, and the patient recovered uneventfully. She gained in weight and had no return of fever. Blood cultures taken following her discharge from the hospital were sterile.

Although bacterial resistance to aureomycin is not common, it can occur, particularly in conditions like subacute endocarditis, where treatment must be prolonged. Astler and Morgan<sup>4</sup> observed 1 case of *Staph. aureus* endocarditis in which the organism developed resistance to penicillin, streptomycin, and the broad-spectrum antibiotics, each in turn. One case of *Str. faecalis* endocarditis, resistant to penicillin, was controlled by aureomycin and chloramphenicol in combination. Another patient developed *Staph. aureus* pneumonia during penicillin therapy, and again during streptomycin therapy, but responded to aureomycin with marked improvement and normal temperature. Spies and co-workers<sup>71</sup> noted the development of partial resistance to aureomycin in 1 case of staphylococcal endocarditis, but reported complete cure in a second case which had resisted treatment with penicillin.

Levinson and co-workers<sup>41,42</sup> were impressed by the fulminating course, and apparent virulence of the strain, in 6 fatal cases of 9 ill of *Staph. aureus* endocarditis. Of these fatal cases, 5 were treated with penicillin and 1 with aureomycin. One of the remaining patients was cured with penicillin; and 2 recovered following aureomycin administration after penicillin had failed. *Staph. albus* was the infecting agent in 9 other cases, of which 6 were fatal. All had been treated with penicillin, since aureomycin was not available at that time. One of the cured cases was treated with both aureomycin and penicillin, with rapid response. Three cases of *Staph. albus* bacteremia were given aureomycin with excellent results.

Naussac and his colleagues<sup>53</sup> preface their report of 3 cases of infectious endocarditis successfully treated with aureomycin, by

saying that even with modern methods of treatment, the death rate in this disease remains between 50 and 75 per cent and that their first experiences with aureomycin have been satisfactory.

The prognosis for 2 of their cases was exceptionally grave. One patient with congenital heart disease had obvious renal damage and repeated pulmonary embolism, even during penicillin administration. The organism could not be found in the blood stream, and treatment was begun late. In the second patient, endocarditis developed in a previously normal heart, following an attack of otitis and a severe sore throat. One of the earliest manifestations was a meningeal embolism, which occurred while penicillin was being given. Here, too, blood culture was negative. The third patient was a woman with aortic insufficiency, hypochromic anemia, and nephritis with microscopic hematuria. The Wassermann was negative, and blood culture yielded *Staph. aureus*. In all cases, treatment was instituted according to the authors' usual practice, with 10 million units of penicillin daily.

The effect of penicillin was only partial and temperatures remained above normal. In the first and third cases, aureomycin brought about apyrexia in 24 hours. The second case, still febrile after 3 weeks of penicillin, required 35 Gm. of aureomycin (3 Gm. initially, 2 Gm. daily thereafter) to reach normal temperatures. The general condition of the patients improved as the fever dropped. Anorexia and anemia disappeared and weight and strength increased rapidly. Penicillin had little effect on the nephritis, but in both cases it disappeared during aureomycin administration; and splenomegaly regressed. No further heart damage was observed; and no embolic phenomena appeared after aureomycin was started.

The patients, observed for 9, 8 and 7 months after interruption of all medication, have remained in good health with no apparent progress of the cardiac lesion. Splenomegaly has completely disappeared. The authors consider themselves justified in assuming cure in all 3 patients. They believe that success in the treatment of



bacterial endocarditis rests as much on the reaction of the tissues to the antibiotic used, as on the sensitivity of the infecting organism, and that from this standpoint, aureomycin is the remedy of choice. Not only is it active against a great variety of bacteria, but its beneficial effect in cases with negative hemoculture indicated that it is well received by the tissues.

Feeling that the succession of antibiotics in their cases had an influence on the outcome, they recommend a 2-stage form of therapy for all cases: initial massive penicillin treatment (250 to 300 million units in 15 or 20 days), followed by aureomycin alone, 3 Gm. daily for 20 days, then 2 Gm. daily for 20 more days, until a total dose of 100 Gm. has been given.

Spink<sup>72</sup> has described a case of acute staphylococcal endocarditis which had been treated with massive doses of penicillin without affecting the bacteremia. The staphylococcus was found to be a penicillinase-producing strain, which required 500 units of penicillin per cc. for inhibition of growth. Growth was inhibited by 1.9 micrograms per cc. of aureomycin, which was then given intravenously. There was immediate improvement in the patient's condition, and subsequent recovery. Aureomycin is perhaps the most potent antagonist to the staphylococcus that is at present available.

In a patient with *Str. viridans* endocarditis superimposed on congenital heart disease, treated by Pflanz<sup>57</sup> with aureomycin, sterility of the blood culture was promptly obtained; and 4 blood cultures done during the next 6 weeks remained sterile. Penicillin had previously been able to produce only temporary sterilization of the blood.

Friedberg<sup>23</sup> reports cure following aureomycin therapy in 2 young patients, both treated early. The pathogen in both cases was *Str. viridans*. Cure with aureomycin was obtained also in 2 cases in which the pathogen was not isolated; both patients were free from renal insufficiency or gross embolism when treatment was begun, and the cardiac condition in both was compensated.

Of the 11 patients treated with aureomycin, 2 died. In one of these, the condition was caused by *S. viridans*; in the second, blood cultures were persistently negative. In both cases, death was due to the cardiac condition; advanced congestive heart failure and auricular fibrillation in 1; and probable massive pulmonary embolism in the other. The 5 remaining patients did not respond completely to aureomycin, but were later cured by penicillin or by combined antibiotic treatment. Aureomycin administration was generally followed by prompt improvement, disappearance of fever and disappearance of organisms from the blood stream. However, except in the 4 cases mentioned, evidence of infection reappeared within 3 to 7 days after stopping treatment. Friedberg believes that aureomycin is best regarded as an aid to the penicillin treatment of endocarditis. It should be used where the infection fails to respond to penicillin; or, where it is caused by organisms resistant to penicillin; or, in endocarditis caused by sensitive Gram-negative bacilli; or, in combination with other antibiotics, when such combination is found to be most effective by *in vitro* tests.

Septic thrombophlebitis may follow intravenous injections made without aseptic precautions, and accounts for the staphylococcal tricuspid valve infection that sometimes occurs in heroin addicts. The first intimation may be given by septic pulmonary embolism, which may be interpreted as pneumonia. These cases usually respond well to antibiotics, because they are seen early and there is no other serious complicating disease. Hussey<sup>34</sup> described a case in which the organism became resistant to penicillin, given in massive dosage with caronamide. The patient had several episodes of pulmonary infarction, with signs of cardiac decompensation and splenomegaly. Cure followed administration of 3 Gm. of aureomycin daily for 7 weeks.

In 2 cases of *Str. viridans* infection, recorded by Kane and Finn,<sup>39</sup> aureomycin brought about cure. In 1 of these cases, penicillin was used as well. Albers<sup>1</sup> reported that endocarditis developed in an eleven-year-old girl with brucellosis. The precise

etiology of the heart lesion was uncertain: *Str. viridans*, but not brucella, was cultured from the blood. On the basis of this finding, penicillin was given without benefit for 3 weeks. Aureomycin was then started. A transitory Herxheimer reaction took place on the third day, followed within 24 hours by striking improvement and subsequent recovery.

Enterococci are notoriously resistant to antibiotics, but many strains are sensitive to aureomycin.<sup>25</sup> Roberts and Goldberg<sup>63</sup> succeeded in producing apparent cure in a case of *Str. faecalis* endocarditis that was resistant to penicillin, chloramphenicol and streptomycin, but sensitive to aureomycin. Aureomycin (2 Gm. daily for 45 days) produced complete remission, but the patient relapsed 12 days after it was discontinued. Aureomycin treatment was resumed, together with penicillin and dihydrostreptomycin, and continued until blood cultures had been negative for 5 months. Four months after discharge, the patient was still clinically well.

Moreau and co-workers<sup>51</sup> have described a very interesting case of bacterial endocarditis, whose first manifestation was a meningal syndrome resulting from a cerebral hematoma. The patient had several convulsions after lumbar puncture, and went into coma. Ventricular puncture revealed a cavity filled with old blood, which was evacuated without benefit; 3 days later, the cavity was emptied surgically. The impression at that time was of an underlying brain tumor. All neurological signs cleared up within a week, but the patient remained tired, pale and anemic, with persistent low fever. The presence of a soft apical systolic murmur, in conjunction with the above findings, suggested bacterial endocarditis. Blood cultures yielded a typical enterococcus, only slightly sensitive to penicillin and streptomycin, but very sensitive to aureomycin. Therapeutic trial of 2 to 8 million units of penicillin gave no result, even when 2 Gm. daily of chloramphenicol was added. Apparent restoration to health followed institution of aureomycin therapy (1.5 to 2 Gm. daily). The temperature became normal, the sedimentation rate dropped, the anemia disap-

peared, blood cultures were negative, and the patient gained 5 Kg. in 9 weeks. Aureomycin was given for 6 weeks to a total of 84 Gm.

Roberts and Goldberg<sup>63</sup> have described another case of enterococcal (*Str. zymogenes*) endocarditis, treated with large amounts of antibiotics over a period of 72 days. Penicillin was ineffective; terramycin produced improvement, but was poorly tolerated and had to be discontinued; aureomycin given intravenously controlled the infection and seemed to sterilize the vegetations.

Giraud and co-workers<sup>27</sup> remark that it may be months before the enterococcus can be demonstrated in culture. None of the previously used remedies, including penicillin in high dosage, has had any effect, but aureomycin usually arrests the course of the disease in a few days. They observed 1 case in which aureomycin was promptly successful after a long period of failure with other remedies. In this case, even after sterilization of the lesions by aureomycin, the arteriolar damage done by the enterococcus was evidenced in various ways and most strikingly by a transitory lupus erythematosus, the condition being closely similar to Libman-Sacks disease.

Raynaud and d'Eshougues<sup>60</sup> described a case of abacteremic infectious endocarditis, which was ushered in after some weeks of progressive weakness and loss of weight and appetite, by an extremely severe generalized polyarthropathy. When the patient was first seen, the heart sounds were dull, but there was no sign of valvular disease. Sodium salicylate and penicillin were prescribed but brought little relief. Two weeks later, the authors saw the patient again because of the appearance of a generalized urticarial eruption with increased fever and general toxicity. At that time, a systolic murmur was heard in the aortic region and the blood pressure was low. The diagnosis rested between an acute severe articular rheumatism and a subacute infectious endocarditis, with the weight of evidence in favor of the former. Treatment with penicillin and heparin was without effect. Blood cultures were persistently negative. The patient was now in a precarious state, and in

the aortic region a diastolic murmur was present, in addition to the previous systolic murmur. There was general enlargement of the cardiac outline. Penicillin administration was intensified, 4 million units being given daily, to a total dose of 254 million units in a little over 2 months. This high dosage brought about relief of arthralgia and of sweating, decrease in fever and improvement in the skin lesions. Within a week after the last dose, the temperature rose again and the joint manifestations returned, although the patient's general and cardiac condition was greatly improved. However, electrophoretic examination of the plasma proteins showed continuing activity of the disease process. All previous therapy was then discontinued and aureomycin was given for a week. At the end of this time, the patient was in excellent condition, and electrophoretic analysis of the serum proteins gave a normal picture. Four months after the end of all antibiotic medication, the patient was back at work, with no complaint except marked stiffness of the joints.

The authors find this examination of the serum proteins to be a most valuable diagnostic and prognostic aid. In subacute infectious endocarditis, as in all infectious diseases, the gamma globulin reflects the antigen-antibody reaction, and becomes elevated. In endocarditis with negative hemoculture, the rise is usually particularly marked. Gamma hyperglobulinemia is also found when the congested liver of heart disease has become unable to ensure the normal metabolism and equilibrium of the blood proteins; the same is true in cirrhosis and certain forms of hepatitis. On the other hand, a rise in the alpha globulin is a specific sign in rheumatic disease and in myocardial infarction, since the level of this globulin depends closely upon the fibrin content of the blood, which rises in inflammatory and necrotic processes.

Metzger and Blum<sup>50</sup> have presented an unusual case of infectious endocarditis with hemolytic crises, in which salicylates, penicillin, streptomycin and chloramphenicol were without effect, and in which aureomycin was successful. The patient was a young

woman who had suffered from rheumatic heart disease for 3 years. Persistent loss of weight, dyspnea, palpitation, cough, irregular menstruation and edema of the malleoli caused her to be admitted for examination. Although the diagnosis of endocarditis lenta was entertained, the absence of positive blood cultures and the severity of joint pains caused her to be treated for the rheumatic condition. Within 3 months the patient had 4 hemolytic crises, characterized by extreme oliguria, albuminuria, and uraturia. Courses of penicillin, streptomycin, and chloramphenicol were given in succession without result. The replacement of these antibiotics with aureomycin brought about cure, and 3 months later the patient was in good health. Eight months afterward, she returned with a new infection which again responded to aureomycin. A few weeks later, she suddenly experienced intense precordial pain. Examination showed extremely rapid pulse, low blood pressure, pericardial friction rub and ventricular tachycardia. The patient left the clinic at her own request and died shortly after reaching her home.

Donzelot and co-workers<sup>19</sup> have discussed a case of infectious endocarditis which was maintained afebrile for 1 year by aureomycin (850 Gm.), and which was finally cured by a combined antibiotic therapy. The pathogen was an enterococcus which was very resistant to penicillin. Penicillin and streptomycin together were able to reduce the temperature temporarily, and when aureomycin was added, the temperature became normal in 48 hours. When aureomycin was discontinued the blood culture again became positive. Association of streptomycin and terramycin also brought normal temperatures and negative hemocultures, but bacteremia returned after it was stopped. For the next 10 months, the antibiotic treatment consisted of the use of aureomycin alone; 1 Gm. daily was the minimum dose capable of maintaining apyrexia and negative hemocultures. However, each time it was stopped the fever mounted again and the blood cultures became positive. The combined use of terramycin and staphylococcus antitoxin had no result. Careful sensitivity tests were then carried

out and on their basis, treatment was instituted with aureomycin, chloramphenicol and streptomycin in association, 2.5 Gm. of each being given in 24 hours. Combined treatment was pursued for 45 days, at the end of which time the patient appeared to be cured. Nine months later, there had been no recurrence. The authors note that, although the antibiotics have a bacteriostatic rather than a bactericidal action when used individually, combinations of 2 or more may show bactericidal activity, a prerequisite for the successful treatment of bacterial endocarditis. They believe that while determination of the bactericidal activity of antibiotic combinations is not feasible in every case of endocarditis, it should be done in very difficult cases.

## *Lymphangitis*

Infectious lymphangitis is almost invariably the result of invasion of the vessel wall by organisms carried in the lymph flowing from a distal infectious process.

Lymphangitis may occur alone, or in association with phlebitis, and may be followed by lymphedema. The portal of entry of the infection is sometimes minute and even careful examination may fail to reveal it. Usually, lymphangitis will subside after adequate drainage of an infectious process; but in many cases chemotherapy is necessary to clear up both the original lesions and the secondarily affected lymph vessels and glands. For this purpose, aureomycin is highly effective.

Logan and co-workers<sup>45</sup> obtained excellent results in 42 cases of cellulitis, with and without lymphangitis. In only 4 of these cases was drainage needed after the first day of aureomycin administration. In 5 patients with acute primary bacterial lymphadenitis, aureomycin brought the infection under control within 3 or 4 days. In every case, fever, pain and toxemia rapidly receded.

In a case of human bite treated by Logan and co-workers<sup>46</sup> with aureomycin, lymphangitis extending from the hand to the axilla cleared up after 2 days of treatment. The lymphangitis that

usually accompanies ulceroglandular tularemia has been observed to clear within 72 hours after the administration of aureomycin, simultaneously with other evidences of infection.<sup>64</sup>

Aureomycin has been found valuable in mastitis, particularly when given in the first 2 or 3 days of the lymphangitic stage. Bantillon and Gabriel<sup>6</sup> note that it will bring about cure of the lymphangitis in 3 to 5 days.

Similar observations have been made by Brochier, Rochet and Noel<sup>9</sup> and by Hervet and Torre.<sup>32</sup> The latter authors found that, in 8 cases of post-partum mammary lymphangitis, aureomycin produced cure in 48 hours. In 3 of these cases, an abscess formed and had to be incised; in the remaining 5, abscess formation was aborted. The equally favorable report of Brochier and co-workers<sup>9</sup> describes the arrest of infection and the disappearance of infectious foci under aureomycin therapy, in 4 patients with simple lymphangitis, 6 with lymphangitis accompanied by deep induration, 1 with lymphangitis and galactophoritis, 8 with deep induration and subcutaneous edema; as well as in 1 patient with a deep infectious nodule, with galactophoritis but without lymphangitis.

## *Pericarditis*

*Acute Nonspecific Pericarditis*—Of the cases of pericarditis treated with aureomycin, mentioned in the literature, most have taken the form of acute nonspecific pericarditis, a disease of unknown (possibly viral) etiology. This disease, which is usually benign and self-limited, is often preceded by an upper respiratory infection, but is apparently not of rheumatic origin. Treatment with sulfonamides, penicillin or streptomycin has not been shown to be of value in benign pericarditis.<sup>65</sup>

Taubenhaus and Brams<sup>75</sup> have reported the results of aureomycin therapy in 3 cases, because they felt it desirable that other observers should be led to examine this method of treatment. In 1 case, treatment with aureomycin was begun early; in the other 2,



only when ordinary therapeutic measures, including the use of other antibiotics, had failed, and the condition of the patients was becoming progressively worse. Improvement was prompt and impressive; systemic toxicity was relieved within 24 hours, before there had been any appreciable change in the physical findings, and recovery was complete in each case. Rosenow and Cross<sup>65</sup> report dramatic clinical response to aureomycin in 2 cases, without apparent effect on the abnormal structural changes present. Brown<sup>11</sup> has reported a severe case which apparently responded well to aureomycin.

Stamps<sup>74</sup> has presented 2 cases suggesting that there may be a tendency towards recurrence in nonspecific pericarditis. Both patients had fever and repeated attacks of severe pain in the chest lasting 48 hours or more. One became afebrile within 24 hours when given aureomycin, but the clinical course of the other case showed little alteration as compared with previous attacks.

The chief importance of acute benign pericarditis, apart from the severe but temporary incapacity caused by it, is the possibility of mistaking it for myocardial infarction. The comparative youthfulness of the average patient, and the exacerbation of pain produced by deep breathing should suggest the correct diagnosis. Dyspnea and orthopnea without lung congestion, and the sitting or leaning position assumed by the patient in his attempt to obtain relief of pain, are characteristic signs. While a pericardial friction rub may be observed in myocardial infarction, it is uniformly present early in the illness in acute pericarditis. It may be audible for a brief time only, and is easily missed if not sought for carefully. Profound shock is not a feature of pericardial, as it is of myocardial, disease.<sup>65</sup>

*Bacterial Pericarditis*—The clinical importance of purulent pericarditis rests on 3 facts: that it may occur as a complication of other infectious diseases; that since it is rare, it may easily be overlooked; and that it is nearly always fatal if not treated. Wilkins and co-workers<sup>78</sup> report a case of *H. influenzae* pericarditis in a four-year-

old boy with a recent history of sore throat. After a week of penicillin treatment, the child was critically ill, and was seen by the authors in consultation. Massive pericardial effusion was present and paracentesis yielded 200 cc. of thick yellow purulent liquid. Penicillin was instilled into the pericardial sac. On the next day pericardiotomy was performed, to remove a large quantity of residual fluid. On identification of the organism on the first postoperative day, dihydrostreptomycin and a sulfonamide combination were given. The temperature postoperatively was 103°F. On the second postoperative day, aureomycin was started and by the next day, the temperature had returned to normal levels, although the pulse still remained rapid. Although the child remained afebrile, the pulse did not slow, peripheral edema persisted, and there was recurrent effusion into the pericardial sac. Following repeated thoracenteses, which produced only sterile fluid, the patient became asymptomatic, and 5 months later appeared completely healthy. The authors emphasize the extreme importance of early diagnosis and suitable treatment, in order to procure immediate recovery and to prevent the later onset of constrictive pericarditis.

Taylor<sup>76</sup> has reported the prompt response to treatment with aureomycin of a patient with tularemic pericarditis. The patient, who on admission had a massive pleural effusion, was started on streptomycin therapy but went rapidly downhill and showed evidence of congestive failure. Pericarditis was found to be present and the patient was digitalized and started on aureomycin. The viscosity of the intrapericardial effusion made adequate evacuation impossible. Marked clinical improvement was evident in 24 hours, and prompt recovery followed.

A case of unusual interest has been reported by Zoeckler,<sup>81</sup> showing the remarkable results of suitable antibiotic therapy. This was an *Actinomyces bovis* invasion of the chest wall, with extension to the heart and the production of clinical pericarditis. Electrocardiographic changes suggested "chronic pericarditis." No involvement of other regions was found. Penicillin was given for 32

days, with some improvement. Aureomycin (2 Gm. daily) was then administered for 13 days. The mycete disappeared from the thoracic lesion, and the mass itself dwindled to a slight induration. The patient was discharged 4 days after the end of treatment; and examination 3 months later demonstrated no physical, roentgenologic or electrocardiographic abnormality.

## *Thrombophlebitis*

In thrombophlebitis, inflammation of the vein produces a secondary endothelial reaction, which favors the local development of a blood clot. Intravascular clotting may at times occur without previous inflammatory changes in the vessel wall, but inflammation soon develops at the site of contact. The mechanism is not clear, but probably involves physical and chemical changes in the blood and slowing of the blood stream, as well as endothelial inflammation. Thrombophlebitis may result from direct local mechanical, infectious or chemical injury; or may occur as a complication of systemic disease, or of the puerperium. The factor of bed rest appears to play an important part in these cases. In a third type, which includes thromboangiitis obliterans, "idiopathic" thrombophlebitis, and thrombophlebitis migrans, there is no evidence of previous venous injury or of systemic disease.

In the presence of a penetrating injury which carries in pathogens, or in the presence of a systemic or focal infection from which organisms can enter the blood stream, the clot may become infected. Thrombophlebitis, and particularly infectious thrombophlebitis, has always presented a difficult therapeutic problem.

Innerfield and co-workers<sup>35</sup> point out that the coagulation time in man may be prolonged by emotional disturbance, and that any prolongation reported in human subjects under treatment with antibiotics may have such an origin. Controlled observations, using placebos, are required for valid conclusions to be drawn. In experimental animals, the intravenous administration of aureomycin

produces a transitory shortening of the coagulation time, together with more than 100 per cent rise in AC-globulin, but has no effect on the prothrombin time.

Aureomycin has been found to be a valuable adjunct to other standard methods of therapy in the management of gangrenous or ulcerative lesions, occurring in peripheral vascular disease. Even in diabetic patients with spreading sepsis, it has been able to control infection.<sup>68</sup> A number of cases of infected thrombophlebitis have been satisfactorily treated with aureomycin, many of them having previously resisted treatment with penicillin and other antimicrobial agents. They include cases of venous infection complicating childbirth; following trauma, or burns, or operative intervention; or occurring in the course of systemic infections, such as pneumonia and empyema.<sup>8,36,38,40,45,47,56,58</sup>

From the clinical and even from the pathological standpoint, it is of little value to distinguish between a thrombus which was originally loosely attached to the vein wall and not at first associated with inflammation (phlebothrombosis), and a thrombus which arises as a result of venous inflammation and which is closely attached to the vessel wall. Whatever the mode of origin of the thrombus, the clinical and pathological picture becomes the same within a very few hours.<sup>3</sup>

Because phlebitis is always associated with thrombosis, inflammation of the superficial veins is easily recognizable, and the veins feel like tender, hard cords. In the deep veins, phlebitis and thrombosis can be recognized only by their effects. There is often no physical sign of the condition. Hospitalization and elaborate diagnostic procedures are not necessary in the vast majority of cases. As a rule, the diagnosis can be made on physical examination. It is necessary to determine whether the pain is of vascular origin or due to disease of other tissues such as nerves, muscles and joints; and also, if it arises in connection with a vessel, whether it is a purely local acute condition, or is associated with generalized vascular disease.

The following findings are suggestive of phlebitis of the deep vessels: diffuse tenderness along the course of the involved veins, becoming acute at points where these veins may be pressed on directly; positive Homans' sign; severe muscular cramps. There may frequently be little indication of systemic upset unless bacteremia is present, as evidenced by high fever, tachycardia, elevated sedimentation rate and leukocytosis.

Perreau and Aufauvre<sup>56</sup> have reported 2 cases of post-partum thrombophlebitis, 1 complicated by pulmonary infarction, and the other accompanied by septicemia and by 3 episodes of pulmonary embolism. The latter patient had suffered trauma to a varicose vein in the eighth month of pregnancy and, in spite of prophylactic treatment by sulfonamides, developed grave post-partum infection. The first patient recovered under combined therapy with penicillin and repository heparin, in addition to the classic treatment for pulmonary infarction, but the second one did not respond to penicillin and streptomycin, together with small doses of anticoagulants, and had 2 pulmonary embolisms. Aureomycin was added to the therapy and the dose of heparin was increased. After 3 days, the other antibiotics were stopped. From the third day on, the temperature dropped, but improvement was interrupted by another rise of temperature and a third pulmonary embolism. Treatment was continued, the temperature came slowly to normal, and 15 days later cure was regarded as assured, after an illness of 3 months. The authors feel that this cure must be attributed to the combination of aureomycin and repository heparin, and that aureomycin is indicated for the treatment of post-partum phlebitis.

Pylephlebitis in a young woman, the result of post-partum infection, was treated by Harrell<sup>28</sup> with heparin, dicumarol and aureomycin. The temperature became normal within 8 days and the patient left the hospital to convalesce at home. In this case, penicillin given before delivery, and penicillin and a sulfonamide given for the post-partum infection, had apparently been ineffective.

Logan and associates<sup>45</sup> have presented a case of thrombophlebitis of the axillary and subclavian veins, following laceration of the hand. The accident had taken place more than 7 months previously, and there had been no response to chemotherapeutic and other measures. Chronic lymphedema of the hand and wrist, cellulitis of the arm, subdeltoid bursitis, and periarthrits of the elbow joint had developed. There was no mobility of the affected parts. A culture of the bursa fluid showed *Staph. albus* and a pleomorphic diphtheroid bacillus, both of which were resistant to penicillin and the sulfonamides, and only slightly less so to streptomycin. Low concentrations of aureomycin inhibited both organisms. Administration of oral aureomycin produced improvement, but the drug was discontinued after a few days, and the patient relapsed. Intravenous administration of aureomycin was followed by marked improvement. There was no recurrence of symptoms and motion of the extremity was gradually regained.

Jackson<sup>36</sup> has reported a case of suppurative thrombophlebitis of the femoral vein in a three-year-old boy, who had been admitted for the treatment of a severe scald. The infection, caused by a penicillin-resistant *Staph. aureus*, arose in the incision made for a transfusion. Following aureomycin administration, complete cure resulted within less than 6 weeks. It was not found necessary either to ligate the vein or to use anticoagulant therapy.

Julsrud<sup>38</sup> has reported a very severe case of staphylococcal sepsis, occurring as a sequel to the injection of varicose veins. The infection spread into the thigh, where it produced multiple perforations discharging pus. Treatment consisted of administration of streptomycin and aureomycin, blood transfusion and incision of the localized area of suppuration. In all, the patient received 14 days' treatment with streptomycin (21 Gm.) and 20 days' treatment with aureomycin (30 Gm.). He was discharged in good condition, after an illness of about 7 weeks, and was perfectly well 5 months later.

In a case of streptococcal pneumonia and empyema, which was

complicated by thrombophlebitis of the internal saphenous vein, and in which terramycin produced little effect, Knight and co-workers<sup>40</sup> found that the use of oral aureomycin, intrapleural penicillin, and anticoagulant and sympatholytic drugs, together with thoracentesis and lumbar paravertebral block, produced normal temperatures within 18 hours. Clinical cure was complete within 3 weeks.

Puig and Bertrand<sup>58</sup> have reported a case of bilateral phlebitis, occurring in the course of brucellosis, which became apyrexial in 4 days with the use of aureomycin. They obtained complete cure, except for the sequels of the phlebitis, after a total administration of 52 Gm.

Dicumarol and aureomycin were given to 1 patient who developed a superficial phlebitis in the dorsal vein of the foot, 5 days after operation on the colon. On this therapy, the temperature and the phlebitis decreased and the patient was discharged 2 weeks after the onset of the vascular infection.<sup>16</sup>

Mallet-Guy and co-workers<sup>17</sup> gave aureomycin to a patient with facial phlebitis, whose condition was serious and had been unimproved by penicillin, sulfonamides, streptomycin, Percortin and X-ray therapy. Palpebral edema and chemosis had developed, indicating involvement of the veins in the ocular region. Spectacular improvement immediately followed the addition of aureomycin to the above remedies, on the fourth day of treatment. Two days later, the staphylococcus present in the original lesion on the lower lip was found to be highly resistant to penicillin, and the use of this antibiotic and of streptomycin was discontinued. Six days after beginning aureomycin, the patient had almost completely recovered.

Noting that septic thrombophlebitis, including cavernous sinus thrombosis and thromboembolism, are exceptionally dangerous in children, and frequently determine a fatal outcome to the original disease, De Camp and associates<sup>18</sup> advocate exclusion of the septic focus from the general circulation by venous ligation,

whenever possible, and vigorous antibacterial therapy. They report the recovery of a desperately ill seven-year-old girl, following these measures. The child was admitted to the hospital with generalized peritonitis, the result of a ruptured appendix, and with a right lower quadrant abscess, which was drained. Three days later, massive gastric bleeding necessitated a second operation for repair of a gastric erosion produced by an indwelling suction tube. Evident cerebral damage was present, consequent on a 12-hour period of profound shock before the second operation. The child was kept alive by means of multiple transfusions and the combined administration of aureomycin, penicillin and streptomycin; but a week later, recurring hemorrhage made partial gastric resection imperative. Slow improvement followed but there was still fever and a right femoral abscess was drained. X-rays taken the following day were suggestive of pulmonary infarction, and exploration of the right saphenous vein revealed a septic thrombus extending into and beyond the common femoral vein. After ligation of the inferior vena cava and division of the right lumbar sympathetic chain, physical recovery proceeded satisfactorily. Eight months later, gratifying mental improvement was also observed.

O'Brien and Birney<sup>65</sup> have reported the successful treatment of a case of cavernous sinus thrombosis in a young child, which developed 8 days following an injury to the orbital ridge. Treatment was started with penicillin. Both eyes being involved at that time, the tentative diagnosis was bilateral orbital cellulitis and ethmoiditis. The local and general condition became worse and the child sank into a semi-stuporous state. Blood cultures were positive for *Staph. aureus*. The child was admitted to the hospital in critical condition and penicillin and a sulfonamide were given, with no influence on the downward course. One hundred milligrams of aureomycin were given intravenously, in addition to the other medication, and the following day the edema of the lids was definitely less and the fever had decreased. The child became alert and was able to eat well. From then on improvement was rapid; the



child was discharged after 2 weeks in hospital. The authors remark that the patient's condition changed within 96 hours from an almost hopeless one to convalescence, when aureomycin was given.

## CHAPTER SIX

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## INFECTIONS PRIMARILY INVOLVING THE SKIN AND SOFT TISSUES

THE skin is exposed to injurious influences from without and, by means of its abundant nervous and vascular supply, to psychogenic and material forces from within. Only slightly less vulnerable are the underlying soft tissues.

The diagnostic and therapeutic problems confronting the dermatologist are far from simple. Not only may the same types of reactions be produced by a multiplicity of causes, but varying syndromes, formerly distinguished by many names and considered to be separate entities, are now believed to be different forms of response to the same etiology. Our increasing knowledge of the physiology and pathology of these superficial structures, our recognition of the part played by the mind and emotions in skin diseases, and our better understanding of the changes produced by metabolic disorders and dietary deficiencies, have been fruitful in producing great improvements in diagnosis and treatment.

It is important, in treating skin conditions, to avoid any medication which will cause further damage to the tissues. Every dermatologist is familiar with the effects of overtreatment of dermatologic disorders and the difficulty of restoring the abused skin to a normal condition. Any antibiotic may, by removing the bacteria which inhibit fungus growth, permit the spread of fungus infection; hence it is important that cases suspected of being fungal in origin should be carefully investigated before using antibiotic therapy.

Tzanck and co-workers<sup>206</sup> have reported an interesting method of cytodagnosis, using scrapings of skin lesions. It permits a study of certain aspects of cellular chemistry, especially of the characteristics and importance of the sulfhydryl group. These authors found that such groups are present in large quantity, in the cells of the malpighian layer, in cases of pemphigus; in smaller amounts in herpes zoster (zona); and in small numbers in erythrodermic vegetative pemphigus. The effect of aureomycin on patients with pemphigus or zona is to produce, during and after treatment, a remarkable fall in the sulfhydryl content of the cells of the malpighian layer. If scrapings are taken from an untreated patient, and are subjected to treatment with a solution of aureomycin and a ferric reagent, there is total blockage of the SH-groups. These results suggest that aureomycin is a specific inhibitor of the sulfhydryl groups both *in vivo* and *in vitro*.

Aureomycin is especially indicated in infections resistant to penicillin, when the patient is allergic to penicillin, or when the organism is known to be insensitive to penicillin or streptomycin. It may be used locally, systemically, or in both ways. Mitchell-Heggs<sup>139</sup> states that he has observed no cases of sensitivity to aureomycin when used locally on the skin.

Garnier<sup>72</sup> states that local use of aureomycin is to be preferred in superficial skin infections; but that where the infection extends beyond the superficial layers, particularly where there is regional or systemic involvement, systemic treatment is indicated. At times, use of both methods will give the best results.

Previous Lederle publications have reviewed the clinical experience of many authors with the use of aureomycin in dermatologic conditions. Its effects have been found excellent in infections caused by pus-forming organisms, as for example in acne, pustular psoriasis, erysipelas, cellulitis, as well as in the skin infections following extensive burns.<sup>13,19,20,25,27,32,33,38,47,48,54,59,60,82,89,111,118,133,146,150,151,152,163,166,174,189,194,215,223</sup> Good results have also been reported in lupus erythematosus;<sup>20</sup> in virus infections such as herpes

simplex,<sup>89,90,99</sup> herpes zoster,<sup>18,21,31,55,69,163</sup> Kaposi's varicelliform eruption<sup>11,15,22,155</sup> and molluscum contagiosum;<sup>79</sup> and in diseases of dubious origin, such as pemphigus and erythema exudativum multiforme.<sup>16,36,118,130,145,159,215</sup> In both of the latter, remission has been observed in a number of cases following aureomycin administration.

In a recent article, Viglioglia<sup>210</sup> has stressed the wide applicability of aureomycin to dermatological infections and has discussed his own experiences in cases of herpes zoster, erythema multiforme, infected erythrodermias, sycosis barbae, folliculitis of the bearded region, and retroauricular eczema. He has described the control, after 4 days of aureomycin therapy, of a case of nodular panniculitis (Weber-Christian) with fever and a tendency to relapse, in which penicillin treatment had failed.

Cutaneous infection in the infant, a frequent source of grave complications, is controllable by aureomycin. Boulez and Germain<sup>21</sup> obtained excellent results in 6 of 7 cases, and an eighth child responded to a second course. Felsen and co-workers<sup>67</sup> recommend the use of aureomycin for the prophylaxis and treatment of staphylococcal infections in hospital nurseries, and mention 6 cases with severe local and general complications, which were resistant to penicillin but sensitive to aureomycin.

Livingood<sup>114</sup> states that the preferred antibiotic preparations for local use in pyogenic infections of the skin in children are bacitracin, aureomycin and neomycin. According to him, any one of these antibiotic ointments may be used as a painless first aid measure for the prevention of infection in scratches and wounds.

## *Abscess*

Long<sup>117</sup> states that aureomycin has won for itself the place of antibiotic of choice in staphylococcal infection, the most frequent cause of abscess of superficial tissues.

Beigelman and Rantz<sup>14</sup> observed penicillin resistance in 56 per

cent of 64 strains of coagulase-positive *Staph. aureus* obtained from patients. While there was definite relationship between previous administration of penicillin and the finding of resistant strains, 20 per cent of these strains came from persons who had not been given penicillin.

Lutz and co-workers<sup>125</sup> have studied the sensitivities of staphylococci and have found that most penicillin-resistant strains also resist heavy concentrations of streptomycin and dihydrostreptomycin, but are inhibited by relatively low concentrations of aureomycin and terramycin. Staphylococci, whether penicillin-sensitive or penicillin-resistant, are equally sensitive to these 2 antibiotics. In no case were the authors able to demonstrate any notable resistance to either aureomycin or terramycin.

Ludwig and co-workers<sup>123</sup> reported good results in 3 cases of mixed pyogenic infection of the skin treated with aureomycin. A marked degree of healing was observed in less than a month in a chronic case of perianal fistulae and abscesses, and cure in the 2 others within 10 days. One of the latter had suffered from pyoderma for about 2 years.

Chandler, Schoenbach and Bryer<sup>33</sup> obtained cure of soft tissue infection in 4 infants, aged from 8 days to 5 weeks, following the use of aureomycin. Small abscesses were absorbed without requiring incision.

Shwachman and co-workers<sup>193</sup> report that they have been able to control staphylococcal abscess in a number of debilitated patients and in children with leukemia, in whom abscess development is a frequent occurrence, even when penicillin, sulfonamides and penicillin had failed.

Schoenbach<sup>188</sup> has mentioned the cure in 10 days, with aureomycin, of scrofulous draining sinuses in the neck, of 12 years' duration. Tubercle bacilli had repeatedly been cultured from the lesions.

Localized suppurations should not be treated with antibiotics alone. Turell<sup>202</sup> points out that in pilonidal and perirectal suppu-

tions, antibiotic therapy, if administered early, during the stage of cellulitis, may prevent abscess formation, but that if localization has occurred, early adequate surgical intervention is necessary. Aureomycin is of value in the postoperative management of such lesions.

Elsewhere in this book, abscesses in other tissues are discussed in relation to the body systems in which they occur.

## *Acne*

Aureomycin is an invaluable aid in the treatment of acne, greatly reducing pustulation.<sup>13,159</sup> Remarkable improvement has been observed in cases of confluent and necrotic acne.<sup>47,91</sup>

Andrews<sup>8</sup> states that cystic, nodular and pustular acne will respond to aureomycin, where all other remedies have failed, and mentions 2 severe cases with fever, debility and leukocytosis, which cleared up completely on aureomycin.

Schiff<sup>186</sup> has presented the case of a man with acne keloidalis, which had begun 28 years previously on the back of the neck. Frequent recurrences with ever wider spread resulted in involvement of the arm pits, scrotum, buttocks, groins and upper thighs. Pain and stiffness, increasing during the past 2 years, had forced the patient to stop working. When first seen by the authors, he was unable to walk and was suffering intense pain in both gluteal regions, with much blood-stained purulent discharge. He was hospitalized and during the next 2 months was given blood transfusions and oral aureomycin. Marked improvement resulted and, while there was still drainage and pain, both had decreased and the patient was able to walk.

Fassotte<sup>64</sup> has reported a case having a combination of epithelioma and acne conglobata in the gluteal region. The infection had gradually extended over a period of more than 30 years, to involve both buttocks and the posterior surfaces of the thighs, with numerous suppurating fistulae from which staphylococcus and *B. pro-*



*teus vulgaris* were cultured. X-ray treatment to the entire region was given, as well as systemic aureomycin. Three months after the completion of treatment, there was complete drying-up of the lesions and softening of the skin, except for an area of necrosis at the top of the intragluteal fold and on the left buttock, caused by irradiation. A crater 3 centimeters in diameter was all that remained of the epithelioma.

In another case of acne conglobata in the same area, of 10 years' duration but uncomplicated by malignant change, Fassotte<sup>65</sup> obtained only temporary benefit from treatment with penicillin, streptomycin, PAS, and a combination of vitamin D and calcium; but what seemed to be permanent cure with aureomycin.

Racouchot<sup>166</sup> mentioned a case treated by Thiers in which a severe and very chronic acne conglobata of the back and buttocks was successfully treated with aureomycin. The lesions rapidly dried and the skin softened. A similar case with deforming involvement of the face and neck responded equally rapidly to synthetic vitamin A. Racouchot notes that the importance of these 2 cases lies in the fact that no previous form of medication has had any manifest effect in this condition.

A recent development in the local application of remedies for skin diseases involves the use of a new type of excipient containing a dioctylsulfosuccinate, antipyrine, propylene glycol, and triethanolamine. This combination has great penetrating power and is a suitable vehicle for antibiotics, antihistamines and precipitated sulfur. The successful use of this substance in polymorphous acne has been reported by Puiggari.<sup>167</sup> The incorporation of an antibiotic in a vehicle of this type might still further improve the results of antibiotic treatment.

## *Anthrax*

Although penicillin, with or without sulfadiazine, is effective in anthrax, the disease also responds readily to aureomycin, with

rapid local and systemic improvement and bacteriologic cure.<sup>74,178</sup> It is advisable to consider the possibility of this infection in unusual looking furuncles, and to test the diagnosis by smear and culture.

Ruiz Sánchez and associates<sup>178</sup> treated 2 cases with very favorable response. There was rapid local and general improvement, and fever disappeared within 3 days. Gold and Boger<sup>74,75</sup> gave aureomycin to 4 patients with anthrax contracted from processing wool or goat hair, very marked improvement resulting in 48 hours. On the fourth day of therapy, in 1 case, the eschar was dry and free from anthrax bacilli, and edema and adenopathy had disappeared. The total period of disability was about 2 weeks. The clinical results in these patients compared favorably with those observed with penicillin.

Phillips<sup>161</sup> mentions a case, reported to the State Laboratory in 1950, of a wool-washer with an anthrax lesion on the back of the neck which responded to penicillin and aureomycin; and Dignam<sup>61</sup> reported rapid healing and uneventful convalescence following aureomycin therapy, in a patient working in the wool-washing department of a carpet company.

Doig and Gemmill<sup>52</sup> have reported on 4 cases of anthrax, all of which were directly or indirectly traceable to a single shipment of hides from India. Three of the cases occurred in Glasgow, 2 of them in employees at a tannery, and 1 contracted in a barber shop patronized by these 2 patients. Two of the 3 cases responded well to penicillin, but the third, which was extremely severe, appeared to be penicillin-resistant. The patient began to recover slowly when given treatment with anti-anthrax serum and aureomycin.

## *Bites*

Unusual danger of infection attaches to the bites of animals, and particularly to those of human beings. The injury is deeply inoculated with a mixed type of infection which produces extensive necrosis and cellulitis. If the patient is seen within 6 hours, Rhoads<sup>170</sup>

recommends complete excision, if feasible. When the bite occurs upon the hands, as is often the case, and it is therefore necessary to save as much tissue as possible, the wound should be laid wide open, thoroughly cleaned, and packed.

Logan and co-workers<sup>115</sup> have successfully used aureomycin in the treatment of 2 cases of human bites of the hand. One of these patients, whose injury had been received 8 days previously, had been given 600,000 units of penicillin in oil at 2-day intervals for 6 days before admission. In this patient, the dorsum of the hand and forearm was red, swollen and tender, with an ulceration about 3 centimeters in diameter situated over the head of the third metacarpal. The ulcer base was gray and necrotic and the extensor tendon was exposed. The patient was unable to flex the involved finger. *Streptococcus viridans*, a gamma streptococcus and a micrococcus were isolated from the ulcer. Eight days of aureomycin treatment, at first intravenous, then oral, resulted in complete healing and a full range of motion in the finger.

Human infection with *Pasteurella multocida* may be more frequent than is usually realized. In the past 5 years, at least 25 cases have been seen at the Mayo Clinic. Neter<sup>148</sup> has reported 4 cases of *P. multocida* infection in children following injury by dogs, cats, or horses. One six-year-old boy, whose infection followed a dog bite on the leg was treated with aureomycin ointment. The wound, from which *P. multocida* and coagulase-positive *Staph. aureus* were cultured, healed satisfactorily and uneventful recovery followed.

## *Burns*

The chief emphasis in the modern management of burns is, of course, on correction of the physiopathologic changes brought about by extensive surface damage, including shock. Local treatment of the burn should be addressed primarily to prevention of fluid and protein loss and preservation of viable epithelium, and secondarily to prevention of invasion of the burned tissues by

bacteria. The oral administration of aureomycin will tend to prevent or control both localized and generalized infection, thus preventing the deepening of shock, but antibiotic therapy cannot be expected to suppress wound suppuration if necrotic material is present. Evans<sup>63</sup> has used aureomycin effectively in preliminary studies on burns.

Leven<sup>111</sup> noted striking results from aureomycin therapy in a child with extensive, badly infected burns, who had developed pyemia and osteomyelitis of the mandible. Although given the standard type of therapy, the child proved sensitive to penicillin and the sulfonamides and was in an apparently hopeless condition. Aureomycin rapidly produced normal temperature and clinical improvement, so that she was soon ready for skin grafting.

Pulaski<sup>168</sup> noted that, in spite of parenteral penicillin, wound suppuration with fever developed in 11 of 38 patients with fresh burns admitted directly to the hospital, and in all of 12 other patients who arrived 7 days or more after injury. Hemolytic streptococci do not, he believes, present a serious problem when the burned patient receives penicillin. In nearly every instance of wound suppuration, there was isolated a coagulase-positive hemolytic *Staph. aureus*, accompanied in about 50 per cent of the cases by pseudomonas, proteus or aerobacter organisms. Fifty per cent of the staphylococcal strains were found to be resistant to penicillin, but less than 10 per cent were resistant to aureomycin or chloramphenicol.

Ludwig, Spier and Wolff<sup>123</sup> reported very satisfactory results with aureomycin ointment in 2 cases of severe and extensive infected burns, involving both head and body. In 1 case with second degree burns, comparison made between an area treated with aureomycin and others treated with penicillin showed clear-cut superiority of the former antibiotic, which rapidly produced a healthy granulating surface; while the penicillin-treated lesions continued to exude seropurulent fluid, and showed no tendency toward epithelization. The second case, with second and third de-

gree burns involving about 32 per cent of the body surface, and with toxic delirium, was given penicillin, an antihistamine, methionine and digitoxin. Aureomycin was applied locally. The sensorium cleared and the fever dropped by the fifth day of treatment. After 2 weeks of therapy, necrotic tissues had separated, leaving a clean-looking surface. The authors, being chiefly concerned with the effects of aureomycin ointment on the infected surfaces, do not mention skin grafting, but it is assumed that this was performed as soon as the condition of the burned area was favorable. On the patient's release after nearly 3 months of hospitalization, the skin defects had healed, leaving scarcely perceptible scars.

Lund<sup>124</sup> believes that studies on the use of antibiotics on burns, particularly atomic bomb burns, are of the utmost urgency. He considers that their well-known ability to control the organisms which cause the most serious infections in burns makes their prompt administration in full dosage completely logical. Aureomycin's potency when given by mouth renders it particularly useful for mass treatment.<sup>28</sup>

One of the common contaminants of burns, as observed by Jackson and co-workers,<sup>94</sup> in Glasgow, is *Strep. pyogenes*, colonization by this organism being productive of delayed healing, skin-graft failure, local sepsis, skin eruptions, and occasionally blood stream infection. *Strep. pyogenes* was present on the burn in 3.9 per cent of admissions. This infection also developed in 16 of 56 patients who were receiving 1 million units of penicillin daily.

In controlled trials, they found that oral administration of aureomycin was more valuable than local or systemic penicillin in preventing *Strep. pyogenes* infection in burns, and was an improvement over penicillin or dibromopropamidine, in controlling established streptococcal infection. The organisms could often be eliminated in as little as 4 days. Thus far, all the strains tested have been sensitive. The authors stress the practical advantages of giving medication by mouth, thus doing away with the frequent dressings necessary when local treatment is used. They believe that these advan-

tages are so obvious that further controlled trials are not indicated.

Lowbury<sup>122</sup> states that *Strep. pyogenes* is the most frequent cause of severe consequences in infected burns, other organisms which, to a less extent, produce adverse results being *Ps. pyocyanea*, coliform bacilli, and *Staph. aureus*. For elimination of *Strep. pyogenes*, he prefers oral aureomycin. He has successfully used it as a prophylactic and in the preparation of infected burns for skin grafting.

James and associates<sup>95</sup> have studied the anemia produced by thermal injury, and believe that the extensive hemolysis which occurs, particularly in larger burns, must always be taken into consideration in the evaluation of the patient. The oral administration of aureomycin greatly reduces the amounts of urobilinogen excreted in the urine and feces.

To prevent infection in burns, Wright, Tamerin, Metzger and Garnes<sup>220</sup> begin the oral administration of aureomycin, 0.5 Gm. twice daily, as soon as the patient is admitted. There has been no invasive infection in any patient so treated.

## Carbuncles

While in all localized collections of pus, free drainage, either spontaneous or surgical, must be established before antibiotics can exert their full effect, aureomycin given systemically is a powerful aid in promoting rapid and complete healing. It is active even in the presence of pus.

A young diabetic reported by McKittrick,<sup>134</sup> who developed a carbuncle of the chin, was treated with penicillin for 5 days and with streptomycin for 4 days, without material benefit. The lesion healed after 4 days of aureomycin therapy.

Logan and co-workers<sup>115</sup> used aureomycin in the treatment of extensive and exquisitely tender carbuncle in 2 patients, 1 a diabetic. In each, there was a large surrounding area of induration, in the central area of which pus was draining from many minute foci. In both cases, gamma streptococci, coagulase-positive beta-hemolytic

*Staph. aureus* and *Sarcina lutea* were demonstrable. Both cases healed uneventfully; 1 without surgical intervention, the other after cruciate incision on the fifth day of aurcomycin administration.

Viglioglia<sup>210</sup> observed rapid response in 2 cases of carbuncle of the neck, rendering surgical drainage unnecessary. In these cases, aurcomycin was given both orally and in the form of ointment.

## *Cat-Scratch Disease* (*Acute Benign Regional Adenopathy*)

"Cat-scratch disease," first observed about 20 years ago, is an acute benign infectious disease, characterized by an insignificant primary lesion, with subacute regional adenopathy and suppuration. There is usually a history of a scratch by a cat or a thorny plant, but cats do not appear to be a virus reservoir. Affected persons react to intradermal injection of an antigen prepared from the pus. Recovery is spontaneous, although it may take several months, but it can be definitely hastened by aurcomycin. If given early, aurcomycin will prevent pus formation in the involved glands.<sup>45, 70, 71, 142</sup>

The editor of the "Lancet" remarks<sup>58</sup> that there is little doubt that cat-scratch fever was first recognized as a clinical entity in 1947, during conversations between Debré of Paris and Foshay of Cincinnati, and that it can now claim a place in the textbooks. Both of these physicians had independently observed cases of the disease in previous years and both had prepared a diagnostic antigen for intradermal test. Since the disease cannot be transmitted to cats, it appears that the animal acts as a vector, perhaps carrying the infection on its claws. The editor of the "Lancet" feels that if this condition had existed as long as men and cats have lived in association, it must have been recognized earlier. He believes that it is a new disease resulting from some change in the habits, either of one of the hosts or of the parasite itself.

Their own observations have led Mollaret and co-workers<sup>140</sup>

to the conclusion that this illness is quite frequent, and that it is of comparatively wide distribution. The incubation period appears to vary from 10 days to 1 or 2 months, and the primary lesion usually takes the form of a simple granuloma, or a granuloma with a drop of pus at its center, or even a pustule resembling a small furuncle. Adenopathy is confined to the glands draining the region in which the granuloma occurs. The name originally given to this infection—"cat-scratch disease"—is not strictly applicable. The authors could trace only 21 of 42 cases to infection from a cat. Their experimental investigations have led them to define the causative agent provisionally as a virus related to the virus of lymphogranuloma venereum, but more benign. Debré,<sup>44</sup> in a recent discussion of the disease, points out that in the vast majority of cases there is a history of close association with cats. One of his patients lived in a home which contained 20 of the animals. The disease is therefore more common in children than in adults, and in country rather than in city dwellers. Debré goes on to say that if ill-judged surgical or medical intervention is avoided, the disease will slowly but surely proceed to cure; but that aureomycin seems to be an excellent drug for bringing about almost immediate arrest of suppuration of the glands, and rapid recovery. He mentions the case of a small boy, to whom aureomycin was given after the disease had been present 6 weeks without manifest improvement. The suppurating gland had drained ever since being punctured a week previously, but drainage stopped the day after beginning aureomycin. Within 3 days the gland was obviously diminishing in size. The author feels that if aureomycin had not been given, the course of the disease would have been very much more prolonged.

The lesions of cat-scratch disease may become secondarily infected. Daniels and MacMurray<sup>45</sup> have reported a case in which subacute regional adenitis developed following a cat-bite on the calf of the leg. The primary lesion became infected, and penicillin produced no improvement. Intradermal tests were strongly positive for cat-scratch disease. The infected puncture wounds were



surrounded by inflammation, edema and fluctuation. Incision yielded a serosanguineous liquid, and was followed by moderate improvement; but the infection again began to spread and wider incision showed necrosis of the soft tissues with foul-smelling exudate. The responsible organism was not exactly identified, but was an anaerobic Gram-negative rod. Rapid healing of the wound was brought about by aureomycin.

In a case described by Merklen and Wattedled,<sup>137</sup> swelling of the submental glands followed a cat-bite on the chin, interfering with movements of the head and with swallowing. Three weeks later, the swelling of the glands was considerable, (about the size of a pigeon's egg) and the temperature was elevated, although there was no sign of general infection. One million units of penicillin were given for 3 days, without any effect on the temperature or on the local lesion; oral administration of aureomycin, begun as soon as the intradermal reaction was found to be positive, was rapidly followed by improvement. After 8 days, the primary crusted skin lesion had disappeared, the glandular swelling had diminished by one-half and was no longer sensitive, and the temperature had returned to normal.

## *Cellulitis*

Aureomycin provides very satisfactory control of infection of the subcutaneous tissues.<sup>33,115,194</sup> Among the conditions successfully treated have been acute or chronic leg ulcers, including some in diabetic patients, acute bacterial lymphadenitis, pyoderma of the scalp, human bites, traumatic amputations, urinary extravasation, mastitis, and chronic varicose ulcers.

Of 42 cases of cellulitis given aureomycin by Logan and associates,<sup>115</sup> all were acutely ill, with high fever. Oral aureomycin was given to 21 cases from the start, while the remainder were in such serious condition that administration was begun intravenously. Remarkable improvement took place within the first 24 hours in

every case, and surgery was required by only 7 patients. A case of staphylococcal phlegmon of the nose, with edema of the upper lip and infraorbital region, did not improve after surgical drainage and penicillin therapy. Twenty-four hours after beginning oral aureomycin, the edema had subsided and recovery was assured on the fourth day.

Recovery has been reported by Toole<sup>200</sup> in 2 cases of submaxillary phlegmon of dental origin, following intravenous (and later oral) administration of aureomycin. Penicillin had been ineffectual. The patients were discharged symptom-free, 6 and 8 days respectively, after the start of aureomycin therapy. Versnel and his colleagues<sup>201</sup> have obtained cure of penicillin-resistant oral cellulitis of dental origin; in Ludwig's angina, they use both penicillin and aureomycin.

Green<sup>76</sup> notes that infection in the fascial spaces of the neck is a less difficult problem than it used to be, and that in recent years it has been rare to encounter an infection of the neck, treated by chemotherapeutic agents, which passes beyond the stage of cellulitis. He has used aureomycin successfully in some cases, particularly those in which combined sulfonamide and penicillin therapy had not given satisfactory results. A number of patients with cellulitis responded very well to sulfonamides and antibiotics alone, without requiring surgery.

Neter and co-workers<sup>149</sup> have discussed the treatment of *P. multocida* cellulitis following the kick of a horse. Five years previously, the patient had been admitted to the hospital with a compound nasal fracture, and almost complete loss of the nasal bones and septum. Plastic repair was done at that time. Nearly 5 years later, operation was performed to reconstruct the bridge of the nose and following surgery there was persistent purulent drainage from this area. Cultures of the discharge, on several occasions during the next year, revealed *P. multocida* in pure culture. It was thought likely that this infection had been introduced at the time of the original accident and had lain dormant in the tissues

until reactivated by surgical interference. Aureomycin was given both locally and systemically; and within a few days, the discharge greatly decreased. After a week, the organism could no longer be isolated. Therapy was discontinued after 3 weeks and marked improvement persisted. The organism was not completely eliminated by this treatment; because 2 months later a cellulitis, caused by a hemolytic streptococcus and *Staph. aureus*, developed. Cultural examination revealed a very few pasteurellae in the discharge. Tests showed that the organisms had retained all of their sensitivity to aureomycin.

### *Dermatitis Herpetiformis (Brocq-Dühring)*

Dermatitis herpetiformis appears to respond better to aureomycin than to any other remedy. Marked relief (sometimes complete remission) has been reported following its use.<sup>49,78,154,177,180,204</sup>

Coste and Piguet<sup>40</sup> have described an unusual form of this disease, in which in addition to bullae there was recurrent edema, beginning in the lower limbs and gradually becoming generalized. Aureomycin had no evident effect on the edema, but was remarkably efficient in controlling bulla formation. Striking but temporary benefit was observed in another case, by Duverne and his colleagues.<sup>57</sup>

Longhi<sup>119</sup> observed very marked improvement in 2 cases of dermatitis herpetiformis treated with aureomycin.

Robinson and Robinson<sup>178</sup> gave oral aureomycin to 3 cases of dermatitis herpetiformis, and oral and local aureomycin to 7; involution followed in 6 cases, improvement in 2, and failure in 2. Two cases of dermatitis repens were also treated with oral aureomycin; 1 case was cured, and the other was somewhat improved. They used aureomycin ointment in 18 cases of dermatitis repens, with only 1 failure. The others were cured in 7 to 28 days.

Livingood<sup>113</sup> has also had good results with aureomycin in some cases. One patient who had been maintained in remission on

a sulfonamide for nearly 2½ years relapsed promptly when the drug was stopped. Administration of aureomycin for 3 months brought about such satisfactory improvement in his condition that it was then possible to stop treatment, without subsequent relapse during a 9-month period.

### *Dermatomyositis*

Schmidt and Stürup<sup>187</sup> found that aureomycin caused a remission of myositis in 1 case of dermatomyositis which had been in existence for 10 or more years. The skin changes were not affected and relapse soon occurred. ACTH treatment caused disappearance of the myositis without any definite change in the poikiloderma or in the number of verrucae.

### *Eczema*

Storck and Rinderknecht<sup>199</sup> believe that a number of cases of eczema, whether circumscribed or generalized, result from an allergic reaction to the bacteria resident on the skin. They have given aureomycin either externally, internally, or by a combined method, to a group of cases of eczema, with remarkable improvement in about 50 per cent. The failures were presumed to be caused by other types of allergens or perhaps by psychological factors.

### *Eczema Vaccinatum*

Eczema vaccinatum is the hypersensitivity reaction of allergic skin to the vaccinia virus, and is most frequently seen in allergic children after vaccination or after exposure to a vaccination wound. The reaction may be very severe, with alarming constitutional disturbance. Clinically, it is indistinguishable from Kaposi's varicelli-form eruption which is elicited by the virus of herpes simplex.

Caution is imperative in vaccinating persons with an allergic history, as well as in guarding them against contact with persons

who have recently been vaccinated. Almost invariably the patient with generalized vaccinia has a history of eczema or other allergic skin condition, and the hypersensitive skin seems to behave as a shock organ. Reported mortality rates have varied from 9 per cent to 66 per cent in various series,<sup>132</sup> and the illness usually lasts 2 or 3 weeks, with at least 1 week of extreme discomfort and toxemia.<sup>22</sup> A number of reports have shown that aureomycin causes rapid disappearance of the fever and of the cutaneous lesions, reduces toxicity, and definitely shortens the illness.<sup>22,23</sup>

Polemann<sup>164</sup> has reported striking results from aureomycin administration, in an adult woman with vaccinia inoculata, who had suffered from eczema since the age of 10. Facial edema and fever disappeared within 2 days. Four Gm. of aureomycin, given over a 3-day period, brought about cure.

Although eczema vaccinatum is comparatively rare, several cases appeared in Glasgow at a time of widespread vaccination during the British smallpox epidemic of 1950. Sommerville and co-workers<sup>197</sup> report 10 cases, all of whom had suffered from previous skin troubles. In only one did the condition follow vaccination; the others had been in contact with recently vaccinated persons. Local treatment alone was successfully used in 2 mild cases, another received aureomycin as well; 3 others were only moderately ill, 2 of these seemed to be benefited by penicillin and a triple sulfonamide combination, and 1 responded to aureomycin. One child treated with penicillin and sulfonamides died of overwhelming toxemia and purulent bronchitis; virus encephalitis was suspected but not proved. Dermatitis gangrenosa infantum developed in a severely toxic four-month-old child. Aureomycin, given at the beginning of this stage, produced only slight, temporary benefit. Three other patients with general toxemia failed to respond to penicillin, with or without sulfonamides, but recovered rapidly when aureomycin was given. The authors recommend that, if recently vaccinated persons must be admitted to a hospital, they should be nursed in isolation.

McConachie and Anderson<sup>132</sup> describe the effect of aureomycin therapy in 5 eczematous children with generalized varicelliform eruption, in only 1 of whom was there a history of recent vaccination. All were acutely ill and the prognosis seemed poor. In 4, aureomycin administration was followed by abrupt decrease in fever and clinical improvement. The authors feel that this may have indicated a true antiviral action, as well as an action on secondary invaders, since a similar effect was not seen with penicillin.

King and Robie<sup>102</sup> have reported cure, almost complete in 72 hours, in an extensive primary vaccinia of the eyelids, which developed 2 weeks after vaccination on the upper arm. Aureomycin was given both systemically and locally in the form of eyedrops.

Esplin<sup>62</sup> has observed a case of eczema vaccinatum, which developed in a young woman with chronic but well-controlled atopic eczema, 10 days after the vaccination of her baby. Administration of aureomycin appeared to bring about resolution. On the day following its addition to the treatment schedule, the fever precipitously dropped to normal levels, and lymphadenitis rapidly subsided. The skin lesions gradually disappeared without leaving scars.

## *Erysipelas*

Infection of the skin by hemolytic streptococci, involving the head region in 85 per cent of cases, carried in former days a death rate of about 13 per cent. Therapy with penicillin and the sulfonamides has brought the rate down to about 2.4 per cent, with the deaths occurring mainly in patients older than 60 or younger than 1 year. Aureomycin appears to be at least equally effective.

Brainerd and co-workers<sup>25</sup> reported satisfactory response to aureomycin in 1 patient with erysipelas; and 1 case of beta-hemolytic streptococcal cellulitis, treated by Dowling and co-workers,<sup>54</sup> recovered within 24 hours on aureomycin therapy. Logan and co-workers<sup>115</sup> also obtained rapid recovery in a sixty-six-year-old woman with severe erysipelas of the face. Fever was still present

after 2 days of penicillin administration, and both eyes were shut by edema. On the third day of aureomycin therapy, she was discharged cured.

## *Erysipeloid*

It is not always easy to isolate *Erysipelothrix rhusiopathiae* from the lesions of human erysipeloid, although it is easily cultivated once it has been isolated. The whole thickness of the skin should be included in the biopsy specimen for successful isolation, and the biopsy should be taken from the active spreading edge of the lesions. Even then it is not always possible to demonstrate the organism. Sneath and associates<sup>195</sup> found that in 7 positive cultures, obtained from biopsy specimens from 20 patients, the *in vitro* sensitivity to aureomycin was well within the therapeutic range of this antibiotic. They feel that it is worthy of clinical trial.

Waage<sup>212</sup> has observed "seal finger," a condition bearing a close clinical resemblance to erysipeloid, in 30 fishermen making port in Tromsø, in Northern Norway. The infection is thought to be contracted from seals and is marked by swelling, pain and a glistening appearance of the finger. Treated symptomatically, it lasts about 6 months. In 20 patients treated with aureomycin, cure was complete in a week or 2, unless the joints had become involved, when healing was slower.

## *Erythema Multiforme*

It has been suggested<sup>175</sup> that various multiple symptom complexes, including Behcet's disease, Reiter's disease, ectodermosis plurifacialis and Stevens-Johnson disease, are actually all variants of erythema multiforme exudativum, and should be grouped under the heading of "muco-cutaneous-ocular syndrome" (q.v.). Favorable response to aureomycin has been reported for all these conditions.<sup>77, 78, 104, 156, 207</sup>

## *Folliculitis and Furunculosis*

For infection of the hair follicles, penicillin has hitherto provided the treatment of choice. The increasing numbers of staphylococcal strains resistant to penicillin and the proven efficacy of aureomycin are causing many physicians to prefer the latter. Garnier<sup>72</sup> feels that aureomycin ointment is indicated in infections of the hair follicles.

Aureomycin ointment brought about cure in 5 to 30 days in 24 of 28 patients with folliculitis, treated by Robinson and Robinson.<sup>176</sup> They also observed improvement in 3 cases of kerion celsi during 3 to 6 weeks' treatment with aureomycin ointment.

Hollander and Hardy<sup>89</sup> reported remarkable response of suppurative folliculitis to aureomycin ointment.

Whitlock and co-workers<sup>214</sup> reported satisfactory results in 2 cases of furunculosis treated with aureomycin. Five cases of furuncle, treated with aureomycin ointment by Robinson and Robinson,<sup>176</sup> cleared in 7 to 14 days.

A large furuncle on the shoulder of a three-week-old baby with a pustular skin rash, which did not respond to penicillin and sulfadiazine, and which in fact developed during treatment of the rash with these agents, healed rapidly after incision and administration of oral aureomycin, as reported by Chandler, Schoenbach and Bryer.<sup>33</sup>

## *Gangrene*

deFagonde<sup>46</sup> studied the sensitivity of various anaerobic bacteria to aureomycin and found that certain highly toxinogenic organisms such as *Cl. botulinum* and *oedematiens*, as well as a number of nontoxinogenic species, were highly sensitive. The anaerobes of gas gangrene, other than *Cl. oedematiens*, were moderately sensitive to aureomycin. *Cl. tetani* was inhibited only at high concentrations. There were very marked differences in sensitivity between individual strains.



Aureomycin has proved remarkably effective in preventing the development of gas gangrene in experimentally infected animals,<sup>3,182</sup> although less so in established infection. It was used clinically by Logan and associates<sup>115</sup> in the treatment of 4 cases of gas gangrene, 2 of them occurring after lower extremity amputation in spite of penicillin administration to all 4 cases. Re-amputation was done in the patients with lower limb infections, incision and debridement in the 2 with gangrene of an upper extremity. One elderly woman with arteriosclerotic, hypertensive heart disease died; massive pulmonary consolidation with pleural effusion was found at autopsy. The other patients recovered after administration of 7 to 27 Gm. of aureomycin.

Prevo<sup>165</sup> reports a case of gas gangrene developing in a girl of 2½, after compound fracture of the humerus. Mid-humeral amputation was done as a life-saving measure. The child's condition continued to be very poor after operation, and it was felt that the clostridial infection had spread past the amputation site. She was given penicillin, streptomycin and aureomycin with almost immediate improvement. Normal pulse and temperature were reached in 48 hours and recovery was uneventful. The author and the consultants in this case believe that aureomycin was the principal factor in cure and that the other antibiotics were primarily useful in aiding control of secondary infection. Prevo recommends that aureomycin be given, as well as penicillin and streptomycin, as a prophylactic measure in all cases of compound fracture.

Herrell<sup>84</sup> states that aureomycin is definitely indicated in the treatment of gas gangrene, but that it should be used in combination with antiserum. It is hardly necessary to add that these remedies are of value chiefly as reinforcing the effects of adequate surgery.

Wright and Strax<sup>219</sup> obtained remarkable results in a case of pyoderma gangrenosa treated with aureomycin. This condition was associated with ulcerative colitis, such suppurative and ulcera-

tive skin lesions being not infrequent accompaniments of chronic debilitating infection. Aureomycin not only produced dramatic cure of the surface lesions but improved the bowel condition and general health, to such an extent that it was possible to perform a subtotal colectomy and to restore the patient to normal activity and well-being.

The arteriosclerosis so common in diabetes favors the development of gangrene, which is responsible for 5 to 8 per cent of all deaths in diabetic patients. McVay and Sprunt<sup>135</sup> report excellent response of radiation necrosis in a mild diabetic, following X-ray treatment of a skin carcinoma, when streptokinase and streptodornase were used in conjunction with aureomycin. Pain had been so severe that even the movement of air could scarcely be borne. In another diabetic patient with gangrenous ulcers on the leg, a similar result was obtained. Aureomycin powder was dissolved, with streptokinase and streptodornase, in sterile isotonic sodium chloride solution, and the liquid applied locally every 24 hours. It thickened to a thin paste in about half an hour, making surgical dressings unnecessary. Control of infection in another case of diabetic gangrene was obtained with this same liquid preparation, but about 6 months later the patient died in uremia. It was felt that the ulceration did not play a significant part in the fatal outcome. Amputation was avoided, by means of the above therapy, in another case of gangrenous ulcer in a diabetic patient. Since the patient refused operation, the aureomycin-streptokinase-streptodornase paste was applied; and progressive improvement followed. The patient was soon able to walk without assistance, and it was felt by the surgeons that grafting could safely be done. An advantage to this combined form of treatment of gangrene is that the treatment may be carried out at home by the patient himself or by his family. All available measures for controlling the diabetes and improving the nutrition, both local and general, must of course be taken.

McKittrick<sup>134</sup> points out that diabetic patients fall naturally

into 2 classifications: the patient with diabetic neuropathy who has, characteristically, good circulation; and the arteriosclerotic diabetic, who is prone to gangrene. A peculiarity of diabetic gangrene is its appearance in areas with apparently adequate circulation and in regions other than the lower extremities.

Hollander and Hardy<sup>89</sup> reported cure following local application of aureomycin ointment, in every one of 6 patients with necrosis of the skin, and Shwachman and co-workers<sup>193</sup> reported satisfactory response in 1 patient with a necrotic lesion of the nasal septum.

## *Herpes Simplex*

The topical use of aureomycin has given good results in a number of cases of herpes simplex. Leclercq<sup>108</sup> considers its use to be indicated in all severe cases.

Kalz, Prichard and Surkis<sup>99</sup> successfully treated 6 patients with 1 application of aureomycin in a water-soluble methyl cellulose film, which uses a minimum of the antibiotic and serves both as medication and protective dressing. The aureomycin film is painted on in several layers and may be easily removed with warm water. Complete healing followed in 48 to 72 hours. Other dermatologists who have reported using aureomycin in this condition have found the ointment satisfactory.<sup>81,89</sup>

In a case of acute disseminated herpes simplex, reported by Riddell and associates,<sup>171</sup> aureomycin was given intravenously, 400 mg. daily for 3 days. Within 24 hours, there was a remarkable decrease in constitutional symptoms; and in 72 hours, only slight crusting remained at the site of the original lesions.

In 1 patient with recurrent herpes simplex, who had suffered from the disease for 5 years and had never been free from symptoms for longer than 2 months; and in another case with a 10-month history of recurrent herpes simplex and a maximum remission of 1 month, complete clearing of the lesions was obtained by

Dougherty<sup>63</sup> with aureomycin ointment, and both were still free from lesions 8 months later.

Harding<sup>81</sup> has reported the effectiveness of aureomycin in a case of extensive herpes simplex, following a cold in the head. The eruption involved the entire face, with pronounced orbital edema, enlargement and tenderness of the preauricular lymph nodes, and a fever of 102°F. The local use of aureomycin ointment entirely cleared the eruption by the sixth day, and the temperature was normal within 3 days.

## *Herpes Zoster*

In most cases of herpes zoster, the course is comparatively mild, and is completed in 10 days or so. However, in severe or protracted cases, aureomycin has often been found extremely useful.<sup>18,21,69,88,96,203</sup> Shedrow<sup>192</sup> reports 1 such case in which herpes zoster and varicella apparently occurred simultaneously. The illness was a protracted one, with hemorrhage into the vesicles. Conservative treatment having failed, aureomycin was given with good results. Ten days later the rash had completely receded and the pain had disappeared.

Herpes zoster may follow skin trauma and may appear not only at the actual site of injury but also in any part which has been forcibly twisted or stretched. Klauder<sup>103</sup> refers to 9 such cases in his own experience and notes in regard to one of them that not only the symptoms but the prompt response to aureomycin suggested the diagnosis of herpes zoster.

In an extensive case of herpes zoster of the thorax, Lacroix and co-workers<sup>105</sup> observed almost complete disappearance of the severe pain, the intense pruritus and the vesicular lesions, after less than 48 hours of aureomycin therapy. The pruritus was the first to disappear, having notably diminished in intensity within 18 hours after the beginning of treatment. Aparicio<sup>9</sup> has reported equally favorable results in a similar case.

Leclercq<sup>108</sup> states that, in herpes zoster, aureomycin is a specific medication whose use is demanded by all severe cases. The ophthalmic involvement produced by this virus is discussed in the chapter on "Infections of the Eye."

## *Hidradenitis Suppurativa*

Hidradenitis suppurativa is a chronic inflammatory disease affecting the skin and subcutaneous tissues in the neighborhood of the sweat glands, the secretions of which form an excellent culture medium for certain bacteria and fungi. Various forms of surgical and medical treatment have been used in the treatment of this condition, with unsatisfactory results on the whole. Penicillin has been found effective in the acute stages, but in even moderately advanced cases will not produce healing of the multiple sinuses. Chronic cases are usually considered fit subjects for surgery.

Viglioglia<sup>210</sup> obtained satisfactory response to aureomycin, in all of 8 cases of axillary hidradenitis in nondiabetic patients, which had proved refractory to all previous therapeutic measures. Surgical intervention was not required in any case.

Wright and co-workers<sup>221</sup> have reported favorable results with aureomycin in the treatment of 2 cases. In one of these, the condition had been present for over 17 years, and the patient was weak, underweight and anemic. The involved areas were indurated and extremely tender, and there was profuse purulent discharge from the numerous sinuses. In preparation for surgery, the patient was placed on a highly nourishing diet and given 1 Gm. of aureomycin daily. Pronounced decrease in tenderness and suppuration was observed after 3 days, and aureomycin was therefore continued for a little over a month. At the end of that time, neither pain nor discharge was present, except for a very scanty flow from 1 sinus. Nearly 6 months later, some recurrence was observed, but again cleared promptly on aureomycin. Another patient with hidradenitis suppurativa was also given aureomycin, but it was

not possible to report this case completely, since the patient was so greatly improved after 4 days of treatment that he refused to remain longer in the hospital.

## *Impetigo Contagiosa*

Aureomycin ointment is very effective in the treatment of impetigo.<sup>59,100</sup> Garnier<sup>72</sup> reports a case of an elderly man with a severe attack of impetigo of the chin and neck, accompanied by adenopathy. An attack 7 years previously had responded to classical forms of treatment, but the present attack was resistant to them. Aureomycin ointment gave a spectacular result; in 48 hours all the lesions were healing, and the condition was reduced to a simple erythema.

Solomons<sup>106</sup> treated 57 children with impetigo. Twelve patients with impetigo contagiosa were cured, as were 33 with impetigo secondary to pediculosis capitis. Of 12 cases secondary to atopic dermatitis, 10 were cured and 2 aggravated.

Robinson and Robinson<sup>176</sup> obtained cure in all of 59 cases of impetigo contagiosa, with the use of aureomycin ointment. The shortest time required to produce cure was 3 days, and the longest was 21 days. In 3 cases of bullous impetigo contagiosa, they obtained cure in 4 to 12 days.

Hollander and Hardy<sup>89</sup> treated 18 cases of impetigo contagiosa, follicular impetigo, and other pyodermata with aureomycin ointment and obtained excellent results in all.

Robinson and Robinson<sup>176</sup> reported that in 20 cases of ecthyma, the shortest treatment necessary to produce cure was 6 days and the longest 10 days; there were no failures.

## *Impetigo Herpetiformis*

Impetigo herpetiformis is a rare condition, which is pustular from the beginning, the lesions being grouped in a circinate manner.

The prognosis in untreated cases is very poor, most of those which have been reported having ended in death.

Sheard<sup>181</sup> has reported what he believes to be the first case treated with aureomycin. The patient was a middle-aged man who had for 4 weeks recurrent polyps or pustules, beginning on the scalp, and gradually spreading to include the mouth, throat, genitals and groin. Eating became difficult and painful. The following treatment was ordered: 1 capsule of aureomycin 4 times daily, 1 aureomycin troche every 2 hours, bacitracin ointment on the lesions 3 times daily. On the next day the patient was very much better and refused bed rest. After 4 days, the skin was almost entirely clear, the patient was enjoying his meals, and was persuaded to continue medication only after argument. Four days later there was almost complete healing, and he has since remained well.

### *Infectious Granuloma*

Falls on sandy or gravelled roads may cause silica particles to be ground into the skin. Following such an accident, a granuloma of the skin may appear and may be mistaken for keloid, Boeck's sarcoid or a lichenoid tuberculid. As much as a quarter of a century may elapse between the original injury and the appearance of the granuloma. Ginsberg and Becker<sup>73</sup> observed notable improvement in 1 such case, following therapy with local and systemic aureomycin. Gradual regression of the lesions continued even when therapy was stopped.

Two cases of granuloma annulare have been reported as cured by aureomycin treatment, by Robinson and Robinson;<sup>176</sup> 3 were improved, and a sixth obtained no benefit. The response of ulcerative forms of infectious granuloma is discussed under the heading of "Ulcer."

The beneficial effects of aureomycin on granulomatous lesions of the bowel have been described in the chapter on infections of the alimentary system.

## *Kaposi's Varicelliform Eruption*

This virus infection of the skin may take the form of small herpetic lesions, or may very closely resemble variola. It may be strictly localized or extensively disseminated, becoming in severe cases confluent and gangrenous, and sometimes having a fatal outcome. It occurs only on the basis of pre-existing skin disease, particularly an allergic dermatitis, the diseased skin areas becoming vulnerable to dermatotropic viruses such as those of herpes or vaccinia. The present tendency is to divide the condition into 2 types, giving the name of "Kaposi's varicelliform eruption" to lesions produced by the virus of herpes simplex and that of "eczema vaccinatum" (q.v.) to the lesions produced by the vaccinia virus.

Aureomycin has produced rapid disappearance of fever and skin lesions in febrile toxic cases of this infection, and shortens the period of illness.<sup>11,15,22,23,80,93,109,208</sup> In some of these cases, penicillin had been ineffective.

Landucci<sup>108</sup> treated 1 case of Kaposi's varicelliform eruption with aureomycin, and obtained rapid cure. The patient was a seven-month-old baby with a history of eczema. The onset of the disease was sudden and the child rapidly became gravely ill and profoundly prostrated. The pulse was weak and rapid, the heart tones poorly heard, and there were rales in the chest. No effect was produced by penicillin therapy and the child's condition continued to become worse. Aureomycin was given for 2 days in a dose of 1 Gm. daily, and for the next 3 days 0.75 Gm. daily, followed by 2 more days' treatment with 0.5 Gm. The baby tolerated the antibiotic extremely well, and showed notable improvement in his general condition from the first day of treatment. Further improvement was gradual but steady, until at the end of the treatment period the child was quite well.

McConachie and Anderson<sup>132</sup> state that in 4 of 5 acutely ill children with Kaposi's varicelliform eruption and an apparently poor prognosis, aureomycin was of great benefit. The fifth child



responded to no form of treatment, but aureomycin was not given in this case until the eighth day of illness, when he had already become critically ill. In these 5 cases, previous penicillin treatment had produced no effect.

DiGeorge and Nelson<sup>60</sup> observed the complete recovery, after 4 days' treatment with aureomycin, of an infant with severe atopic dermatitis and Kaposi's varicelliform eruption.

In an eczematous child of 10 months, treated by Kimmig,<sup>101</sup> a generalized pustular eruption developed, shortly after the father had suffered from a cold sore. In spite of penicillin therapy, the eruption spread, and stomatitis aphthosa developed. Aureomycin, 0.5 Gm. daily, was given. On the following day, there were no new pustules and the fever had decreased. During the next 4 days, the temperature sank to normal and the skin condition continued to heal, completely disappearing by the end of a week. The previously existing neurodermatitis was uninfluenced.

## *Lichen Planus*

Only 2 reports on the use of aureomycin in lichen planus have appeared in the literature, as far as can be ascertained.

In 1950, Robinson<sup>174</sup> reported good results in 3 cases, fair results in 5, and 2 failures. The response was considered satisfactory in all but 3 patients. One patient who had suffered from lichen planus for several years without remission, had more benefit from aureomycin than from all previous forms of treatment. Two patients had mouth lesions, which are usually refractory to treatment but which disappeared during oral and intravenous administration of aureomycin.

Recently, in 3 severe cases of lichen planus, of fairly acute development and accompanied by extensive painful mouth lesions, Joulia and his colleagues<sup>98</sup> obtained undeniable benefit, more obvious in the mouth lesions than in the skin manifestations. There

was rapid clinical and subjective improvement of the mucosal involvement, with relief of pain and ability to resume normal food intake.

## *Lupus Erythematosus*

In spite of increasing knowledge regarding lupus erythematosus, therapy remains very unsatisfactory and most, if not all, of the disseminated cases end fatally. Aureomycin has given good results in localized lupus.<sup>146</sup>

Bolgert, Le Sourd and Habib<sup>20</sup> observed an alarmingly severe exacerbation of subacute lupus erythematosus, with hemorrhagic and bullous lesions, which did not respond to ordinary remedies. The administration of aureomycin brought about steady improvement in the general condition and spectacular response of the cutaneous lesions. The temperature rose slightly on the second day, and then dropped by lysis.

Charpy and co-workers<sup>34</sup> report that an acute case of exanthematous lupus with a hemorrhagic syndrome was cured after 16 days of treatment with 6 Gm. of aureomycin daily. In another case, this treatment seemed to exaggerate symptoms and in 1 case of chronic lupus erythematosus, there was no change. This disease was observed to respond both to chloramphenicol and to aureomycin in a case observed by Robinson.<sup>172</sup>

In a severely toxic case of bullous, hemorrhagic lupus erythematosus, clinical recovery followed aureomycin administration in association with Cortin. Bolgert and co-workers,<sup>20</sup> reporting this case, remarked that the patient's grave condition made spontaneous remission extremely unlikely. She was still continuing aureomycin treatment at the time of their report; the local lesions were less marked than they had been before the acute flare-up, and continued to regress.

## *Mastitis*

For the management of infectious breast complications following delivery, aureomycin has been found to be of great value. If given early, it will prevent the development of suppuration, and may at times exert sufficient influence on established suppuration to render surgical intervention unnecessary. In puerperal infections, particularly in mastitis and pycclitis, the staphylococcus has shown progressively increased resistance to both streptomycin and penicillin. Resistance to penicillin is also evidenced by *E. coli*, and to penicillin, streptomycin and the sulfonamides by enterococci. All of these organisms are sensitive to aureomycin.

In 26 cases of acute mastitis, treated at various stages of evolution, Lepage and his colleagues<sup>110</sup> obtained 18 complete cures; 4 partial cures, with persistence of a small residual focus; and 4 failures, in which incision of the abscess could not be avoided.

Napp and Clauss<sup>144</sup> have found that the incidence of penicillin-resistant and streptomycin-resistant staphylococci in the nasal smears of recently delivered women and of other patients, is low during the first 3 days of hospitalization, but later shows a definite increase. This increase in resistance has been observed also in smears from the breasts of the nursing mother and from the mouth of the newborn child. The authors found penicillin-resistant staphylococci in the nose of 38.5 per cent of the physicians and 75 per cent of the nurses, while streptomycin-resistant staphylococci were found in 23 per cent and 3.1 per cent, respectively.

Aureomycin, used in a hospital nursery epidemic of staphylococcal infection, was effective in preventing the appearance of breast abscess in the mothers.<sup>133</sup> Pigeaud and co-workers<sup>162</sup> have used aureomycin in puerperal mastitis, as well as in other staphylococcal infections. The strains which they have encountered have become increasingly resistant to both penicillin and streptomycin.

Breast inflammation occurring after delivery is often slow to heal in spite of the use of sulfonamides, local and systemic peni-

cillin, and X-ray treatment. Hervet and Torre<sup>85</sup> have used aureomycin for about 20 such cases in their clinic. At the first sign of lymphangitis, the patient is given 0.25 Gm. of aureomycin morning and night, and it has usually been possible to prevent the development of an abscess. When abscess formation has begun, aureomycin permits rapid localization in about 48 hours, so that early incision becomes possible. Patients with fully-developed abscesses are, as a rule, cured within 2 days by surgical drainage and aureomycin. The authors list, as advantages of aureomycin treatment, the ability to treat the patients as ambulatory cases, the efficacy of oral medication, the rapid local and general improvement, and the good tolerance exhibited on the whole for this antibiotic.

In a series of 51 cases of breast abscess, Mougenot and Sarlin<sup>143</sup> studied the *in vitro* action of the principal antibiotics on the staphylococcal strains involved. Aureomycin was the only antibiotic found to be efficacious, and this finding was confirmed by the response to aureomycin of 2 cases which had been treated without success by penicillin and streptomycin.

Bansillon and Gabriel<sup>12</sup> state that in their experience penicillin has not only become progressively less effective in the treatment of breast abscess but actually seems at present to prolong its evolution. Aureomycin, they consider, has solved the treatment problem. When given in the first 2 or 3 days of the earliest (lymphangitic) stage, it will effect cure in 3 to 5 days, and acts similarly in infection of the follicles or of the lacteal ducts. In fully developed mastitis, the results depend on the earliness of treatment, the dosage of aureomycin and the period over which treatment is continued. There is usually local improvement and disappearance of fever, but an indurated nodule may persist for weeks. In such cases, if there is freedom from pain and fever, treatment may be discontinued after a total of 15 to 20 Gm. of aureomycin has been given, but the patient should be examined once or twice a week.

Brochier, Rochet and Noël<sup>28</sup> have given aureomycin to patients with infectious breast complications following delivery. In

27 cases of presuppurative and suppurative mastitis, cure was produced. They feel that aureomycin, by permitting the control of these breast infections, will prove an important factor in the removal of foci for the spread of staphylococcal infection throughout a maternity ward. While, of course, breast feeding was suspended on the affected side, the child was again put to the breast when infection was overcome. The authors noted the appearance of mild digestive symptoms and somewhat increased frequency of stools in a few infants, indicating the excretion of aureomycin in appreciable quantities in the breast milk.

### *Molluscum Contagiosum*

The oral administration of aureomycin has given gratifying results in the treatment of molluscum contagiosum.<sup>79,211</sup>

Feiler<sup>86</sup> has reported a case of molluscum contagiosum, not improved by the application of tincture of iodine or of streptomycin ointment, but clearing entirely after a course of therapy with AUREOMYCIN SPERSOIDS\* Dispersible Powder. In discussing this paper, Wolf<sup>216</sup> mentioned that a boy, who had about 300 lesions, was so far improved by 2 weeks' treatment with aureomycin that about 80 to 90 per cent of the lesions had disappeared by the end of therapy.

Using aureomycin ointment, Viglioglia<sup>210</sup> obtained complete cure in 3 days in 1 case of molluscum contagiosum.

In 3 cases of molluscum contagiosum reported by Dougherty,<sup>83</sup> oral ingestion of aureomycin failed to cure, as did local applications.

Robinson and Robinson<sup>176</sup> treated 5 patients with molluscum contagiosum with aureomycin, and reported 1 cured, 1 improved, and 3 having received no benefit.

### *Muco-Cutaneous-Ocular Syndrome*

The muco-cutaneous-ocular syndrome is a symptom complex

\*Reg. U. S. Pat. Off.

characterized by lesions of several ectodermal structures. In its various forms it includes erythema multiforme exudativum. Behcet's disease, ectodermosis pluriorificialis, Stevens-Johnson disease, and possibly Reiter's disease. Whether this syndrome includes a number of clinically similar but etiologically unrelated diseases, or whether it includes a variety of clinical forms produced by the same etiologic agent, is unknown. The symptomatology includes inflammation, ulceration, vesiculation and bulla formation. There may be involvement of the eye, the mouth, the male or female genital tract, the skin, or the joints. A skin rash, maculopapular, vesicular or bullous, is the most constant feature, the structures next most commonly involved being those of the eye. There may or may not be fever, leukocytosis and pneumonic involvement. Any combination of these lesions and sites of disease may be found.

It is more than likely that a combination of factors is responsible for this syndrome and its variants. Robinson<sup>73</sup> has pointed out that the successful use of aureomycin in a number of patients is suggestive of an infectious origin, probably a virus, in at least some cases. Wright and Jenkins<sup>217</sup> state that while there is no evidence that erythema multiforme exudativum is a contagious disease, there does appear to be a tendency for a number of cases to appear in the community shortly after the development of 1 case.

*Ectodermosis Pluriorificialis*—On the basis of a presumed virus origin for certain clinical forms of ectodermosis pluriorificialis, Valdes and colleagues<sup>207</sup> turned to aureomycin for the treatment of the last 3 children with this disease seen by them. Surprisingly good response was noted within 24 to 48 hours; the skin and mucous membrane lesions receded, and the children were cured in a few days. There was neither sequel nor complication, and several months later, there had been no recurrence.

*Erythema Multiforme Exudativum*—Heichmann and Valero<sup>83</sup> suggest that there may be a relationship between an allergic reaction to drugs, vaccinations and other medical or surgical procedures,

and viral infection, in this group of diseases. They discuss the case of a man who developed the Stevens-Johnson syndrome 1 week after vaccination. In contrast to penicillin, which failed to produce any benefit, aureomycin promptly brought down the temperature. Recovery was complete after 6 days of aureomycin.

Nellen and Lang<sup>147</sup> consider that although some cases of erythema multiforme may be traced to bacterial infection, drugs, sera, and other causes, it is possible that these latter factors alter a balanced virus-host relationship in favor of the virus.

Yates and co-workers<sup>222</sup> point out the apparent increase in the severity of erythema exudativum multiforme since it was first discovered nearly 90 years ago. They raise the question as to whether these cases should not be grouped according to the degree of toxicity rather than according to the structures mainly affected.

With aureomycin, rapid recovery was observed by Michel and Nivollet,<sup>138</sup> in a widespread febrile eruption, in which salicylates and penicillin had failed; and by Melick<sup>156</sup> in a case unaffected by sulfonamides, arsenicals and penicillin.

In a case of recurrent bullous erythema multiforme, confining the patient to bed for weeks at a time, Duval and Sebald<sup>56</sup> were able to control successive relapses with aureomycin and restore the patient to full activity.

Nellen and Lang<sup>147</sup> found aureomycin to be markedly beneficial in a case of erythema multiforme gravis. Vesicles, bullae, ulcers and raw areas covered the body, limbs and face, with involvement of the eyelids, lips, gums, palate and tongue. No response followed penicillin therapy, and the temperature rose to 102°F. Extension to the bladder produced extreme dysuria, followed by retention. The patient was moribund when aureomycin therapy was begun, in a dose of 1 Gm. daily by mouth. There was spectacular general improvement in 48 hours, the temperature was normal on the fifth day, and 2 weeks later, the patient was well.

Robinson and Robinson<sup>176</sup> gave systemic aureomycin to 16 patients with erythema multiforme, combined in 5 cases with

aureomycin ointment, and obtained involution in 13, improvement in 2, and failure in 1. Three cases of erythema nodosum were apparently cured and 1 was improved.

*Reiter's Syndrome*—Reiter's syndrome is a clinical entity that includes urethritis, arthritis, and conjunctivitis. It appears to be a hypersensitivity reaction to a variety of pathogens, including fungi, and in some cases apparently to proteins. Korb and Brown<sup>104</sup> have reported 1 case, not responsive to sulfonamides and penicillin, in which intensive aureomycin therapy was followed within 3 days by complete remission of the urethral, conjunctival and joint symptoms. In 3 aureomycin-treated cases reported by Lövgren,<sup>121</sup> there were 2 failures and 1 prompt recovery.

Carroll, Allen and Flynn,<sup>30</sup> obtained prompt improvement, with rapid disappearance of discharge and conjunctivitis, in 1 patient with Reiter's disease to whom they gave aureomycin. Although the arthritis persisted, it was less severe. Addition of Mapharsen to the antibiotic therapy brought about further improvement.

In a 17-year-old male, treated with aureomycin by Griep and Leich,<sup>77</sup> marked diminution in photophobia and ocular pain, disappearance of urethral discharge and fever, and decrease in joint pain and swelling were observed within 36 hours. Nine days after cessation of treatment, the patient was almost asymptomatic and was apparently well 1 year later.

In 1 case of recurrent Reiter's syndrome in a boy of 5, Zureick and Lattaquic<sup>224</sup> found that aureomycin, 750 mg. daily by mouth, cleared up the inflammation of the testes and epididymes in 2 days, the urethritis in 3 days, and the skin lesions in 5.

Huguenin and Alcay<sup>92</sup> describe the successful use of aureomycin in a case of Reiter's syndrome in a young man, who had also a chronic colitis with strongyloidosis. The illness began with an abundant nonspecific urethral discharge and, while receiving penicillin for this, the patient observed edema of the eyelids, lacrimation, and redness of the conjunctivae, together with a torti-



collis which marked the beginning of a rapidly spreading polyarthritis. Considerable improvement followed the administration of chloramphenicol, but a hydrarthrosis present in 1 knee disappeared only slowly, leaving behind it limitation of movement. Arthritis in the left shoulder was much more stubborn, and although the urethritis had cleared up, there was still severe balanitis. Two grams of aurcomycin daily were then given for 8 days. Mild glossitis developed, corrected easily by administration of B complex vitamins. All symptoms disappeared during aurcomycin therapy, leaving only slight atrophy of the muscles of the right quadriceps and of the left arm and shoulder. The parasitosis was successfully treated with thymol. Examination 2 months later showed the patient in excellent health, with a weight gain of 15 pounds and almost complete restoration of muscular function, and completely able to resume normal activities. The authors feel that while the syndrome might be attributable to the colitis caused by strongyloid infestation, the response to antibiotic therapy suggests infection with a filterable virus.

Warter and Prebay<sup>213</sup> have reported 1 case of Reiter's syndrome, which became worse and more extensive during penicillin treatment, and in which neither aurecomycin nor streptomycin proved effective. In view of the many agents which are thought capable of producing this syndrome, it is probable that the hypersensitivity was not a bacterial one.

*Stevens-Johnson Syndrome* — The Stevens-Johnson syndrome is marked by high fever, prostration, bullous skin rash, conjunctivitis, stomatitis, and sometimes involvement of the urogenital mucosa. More rarely, there is involvement of the lung, and the eye lesions may take the form of keratitis or panophthalmitis. In spite of the extreme toxicity which may be present in the Stevens-Johnson syndrome, there are few complications, although relapse is common. Nephritis, nephrosis, bronchopneumonia, stricture of the vagina, uremia, and pyogenic invasion of the skin have been observed, but the most important complications are those affecting

the eye. Septicemia has been reported,<sup>198,222</sup> but whether this is a complication of the primary ectodermal condition or whether, as Starr and Holliday suggest,<sup>198</sup> the erythema multiforme is a cutaneous manifestation of blood stream invasion, is not certain. They reported the recovery of a twelve-day-old infant, with severe erythema multiforme, complicated by the formation of soft tissue abscesses, the pus from which yielded streptococcus. Gradual improvement and ultimate cure followed the administration of aureomycin with penicillin. Another infant (16 days of age) developed erythema multiforme together with *Staph. albus* septicemia and a complicating orchitis. Satisfactory response followed therapy with oral aureomycin and parenteral penicillin.

Striking response to aureomycin was observed by Jones<sup>97</sup> in 3 cases of Stevens-Johnson syndrome. One patient relapsed promptly when aureomycin was stopped, did not respond to a placebo similar in appearance to aureomycin capsules, and again improved rapidly when aureomycin was restarted. The most rapid recovery was seen in the most acute of the 3 cases, who had also pericardial involvement. This patient had completely recovered 5 days after admission, after a total of 6 Gm. of aureomycin had been administered.

A three-year-old child acutely ill with erythema exudativum multiforme, attended by Wright and Jenkins,<sup>217</sup> exhibited within 24 hours after admission the complete Stevens-Johnson syndrome and bronchopneumonia. The next day he was in critical condition, in spite of penicillin therapy, and the skin lesions were worse. Aureomycin was administered and within 4 days the temperature was normal, the skin lesions had begun to clear, and the child became rational for the first time. After the third day of aureomycin, no new lesions appeared. However, another child with the mild form of this disease responded to no therapy, local or general, and remained hospitalized for 6 months on account of frequent recurrences. It is suggested that these 2 variants of the disease are separate entities.

"Cure" with oral aureomycin of 3 cases of Stevens-Johnson syndrome has been reported by Salah and Ghanem.<sup>181</sup> One of the cases had suffered 7 relapses in 2 years, in spite of every known form of treatment, and another had 4 in 1 year.

Torin<sup>201</sup> reports a case of Stevens-Johnson syndrome in a girl of 15, with an herpetiform eruption in the pharynx, larynx, eyes, and labia majora. The patient was unable to swallow and had laryngospasm. No relief was obtained from sulfonamides, penicillin, streptomycin or chloramphenicol, but dramatic recovery followed within 48 hours of beginning aureomycin.

Robinson<sup>173</sup> remarks that the introduction of aureomycin marked a long stride forward in the treatment of the various manifestations of the muco-cutaneous-ocular syndrome. He has had great success with aureomycin given intravenously, and has not observed undesirable side reactions. Uneventful recovery has taken place in a large number of patients with erythema multiforme and its various manifestations, who have been treated with aureomycin, either orally or intravenously.

## *Noma*

Noma, otherwise known as gangrenous stomatitis or cancrum oris, occurs almost exclusively in debilitated patients, and frequently complicates infection in such persons. Measles is a frequent predisposing cause. The death rate may be as high as 90 per cent, particularly in children. Recovery is accompanied by marked deformities. D'Agostino<sup>42</sup> has reported a case of noma in a fifty-year-old woman, with syphilis and cardiac decompensation. Local application of an aureomycin-gelatin preparation was followed in 48 hours by cleansing of the gangrenous area. The rapid extension of necrosis was stopped and the putrid odor disappeared. However, the patient's cardiorenal condition grew worse and she died in uremia.

## *Pemphigus*

The various forms of pemphigus are believed to be, at least in part, of virus origin. Assuming this to be the case, numerous authors have made therapeutic trial of aureomycin with considerable success. Alayon and co-workers<sup>2</sup> have treated vegetative pemphigus and foliaceous pemphigus with aureomycin. In the first group, rapid regression of the cutaneous and mucosal lesions took place and clinical cure was obtained after 43 days of treatment. In the latter group, improvement was observed in 3 cases and almost total regression of the lesions in a fourth. No improvement was noted in 2 extremely grave cases of pemphigus vulgaris.

Often a case which seems to be atypical dermatitis herpetiformis eventually becomes pemphigus vulgaris, and Peterkin<sup>157</sup> suggests that pemphigus vulgaris may be merely a severe dermatitis herpetiformis occurring in the later stages of life.

Bettley and Fairburn<sup>17</sup> observed that aureomycin exerted a beneficial influence on bullous diseases of the skin. Since both pemphigus vulgaris and bullous dermatitis herpetiformis, while suspected to be of virus origin, are not known to be so, the authors suggest that the action of aureomycin may be directly on the cohesion of epidermal cells. They note that in their successfully treated cases, very little secondary infection was present, and that treatment resulted in suppression of the primary lesions, so that the effect was clearly not a mere removal of secondary sepsis.

Tzanck, Steinbuch and Melki<sup>205, 206</sup> believe that at least part of the mechanism of aureomycin action in pemphigus may be its influence on the sulfhydryl content of the cells. It is known that the toxic effects of X-rays are connected with the sulfhydryls of the tissues, that BAL re-establishes the activity of these groups when blocked by metallic poisoning, and that both nitrogen mustard and AMINOPTERIN\* 4-Amino-pteroylglutamic Acid inhibit certain sulfhydryl-containing enzymes. In patients with pemphigus or herpes zoster (zona) who have been treated with aureomycin, the

\*Trade-mark

involved skin is shown to have a much lower content of glutathione, a sulfhydryl-containing substance, than would have been expected in untreated pemphigus. In scrapings taken from untreated patients, the SH-groups can be totally blocked by treating them with a solution of aureomycin and a ferric reagent.

Cordiviola and co-workers<sup>39</sup> have recorded immediate response to aureomycin in a chronic case of pemphigus. The patient suffered from anorexia, asthenia and insomnia; erosive lesions in the mouth and throat rendered swallowing difficult. Previous use of penicillin and of streptomycin had given only partial and temporary relief. Treatment was begun with aureomycin, vitamin B complex and injectable liver extract. Twenty-four hours later, great subjective improvement was manifest. These remedies, in addition to several small blood transfusions, were continued for 1 month. Aureomycin troches were also given for the mouth lesions. At the end of this time oral aureomycin was stopped, and at the end of 2 months the troches were stopped. At that point all of the lesions, cutaneous and mucosal, were cured. The patient was in good health, and had gained 7 kilograms in weight. The ingestion of 90 Gm. of aureomycin over a period of 27 days was perfectly tolerated. The authors feel that in this serious viral infection, it is important to give fairly high dosage of aureomycin, 3 to 5 Gm. daily, since new lesions occurred in their patient when the dose was dropped to 2 Gm. a day.

Panja and co-workers<sup>153</sup> gave aureomycin to 1 case of pemphigus foliaceus. The patient was in a grave condition on admission, with generalized ulceration and edema, and with exfoliative dermatitis covering the entire surface. The fetid exudate necessitated his isolation. Itching was so severe that the patient was unable to sleep; conjunctivitis and purulent discharge were present in both eyes. Penicillin and arsenic administration had no effect, but after 4 days of aureomycin, 1.25 Gm. daily, the fever and skin lesions began to decrease. Within 10 days, the patient's condition was transformed, and 3 weeks after aureomycin had

been started, he had very little evidence of disease.

Longhi<sup>119</sup> has successfully treated 4 cases of pemphigus with aureomycin. The antibiotic was preferably given by mouth, but where this was not possible it was given intravenously or intramuscularly. These patients were all seriously ill and in very poor condition for treatment.

Margarot and co-workers<sup>127</sup> have presented a case of seborrheic pemphigus, which had gradually developed into pemphigus foliaceus over a period of 3½ years, and had been unimproved by any method of treatment. The patient was emaciated, with a septic type of fever; the entire body was raw and covered with foul exudate. Aureomycin therapy was instituted and from the third day the fever dropped, the exudation decreased, the odor disappeared and no new bullae developed. The patient, however, became intolerant to the antibiotic, and subsequent treatment at a lower dosage was not effective.

A patient with pemphigus, presented by Chiamonte,<sup>35</sup> was kept free of bullae for 1 year with 750 mg. of aureomycin daily. Each time that the drug was reduced or stopped, new crops of bullous lesions appeared.

Erger<sup>61</sup> has reported 2 cases of familial benign chronic pemphigus, of 7 or 8 years' duration, which had been frequently but unsuccessfully treated. With 3 capsules daily of aureomycin, both cleared within a week, and have maintained themselves in fairly good condition by taking 1 capsule daily for more than 18 months.

Scholtz and Williamson<sup>190</sup> observed good results from aureomycin, in a case of Senear-Usher pemphigus.

Five cases of pemphigus neonatorum, treated with aureomycin ointment by Robinson and Robinson,<sup>176</sup> recovered within 5 to 14 days.

Although spontaneous remission renders final judgment as to the value of any treatment for pemphigus vegetans uncertain, Alayon and co-workers<sup>1</sup> feel that in a case studied by them and responding with almost total cure, 2 facts were against the hypoth-

esis of spontaneous remission: (a) the remarkable improvement within a few days after beginning aureomycin, the partial relapse which occurred when treatment was interrupted, and the prompt resumption of improvement on restarting aureomycin; (b) the resistance of the lesions presented by the patient to every previous type of therapy.

### *Pinta (Mal del Pinto)*

Pinta, a treponematosi occurring in Mexico and South America, is very closely related to yaws and syphilis, as well as to the comparable disease of the Arabs of the Middle East, "bejel," and may be identical with them. No distinguishable difference exists between the spirochetes causing these diseases, the fundamental pathology of each, or their serologic reactions. The observed variations of the clinical picture may be the result of purely local conditions.

Mazzotti and Olarte<sup>131</sup> administered oral aureomycin to 2 patients with "mal del pinto" and observed the disappearance of organisms from the interstitial fluid which could be obtained by pressure of the skin after excoriation of the epidermis. Further studies on this subject, however, are necessary.

### *Sycosis Vulgaris (Sycosis Barbae)*

Sycosis vulgaris has a tendency to extreme chronicity and is characterized by an amazing amount of resistance to treatment.

Pinne<sup>163</sup> has remarked that sycosis vulgaris, or staphylococcal folliculitis of the bearded region, yields to aureomycin ointment, sometimes with spectacular results, and Saunders<sup>183</sup> reports remarkable benefit from the use of aureomycin in a case of sycosis vulgaris which had persisted for 2 years, in spite of a large variety of treatments. After 6 weeks' local use of aureomycin ointment, the patient's face was entirely clear and had remained so at the time of writing.

Sawicky and co-workers<sup>184</sup> obtained cure in 7 of 18 cases of sycosis vulgaris, improvement in 7, and failure in 4, with the use of aureomycin ointment. One patient developed a mild contact dermatitis. Grund,<sup>78</sup> using oral aureomycin (10 or 12 capsules daily), obtained excellent and prompt results in 9 cases of sycosis vulgaris and in 1 case of lupoid sycosis of the scalp, face and neck. No local treatment was used. All of the cases had resisted every recognized form of treatment, including parenteral penicillin.

Robinson and Robinson<sup>176</sup> obtained cure in 4 to 7 days, in 15 of 16 cases of sycosis vulgaris, following the use of aureomycin ointment. Garnier<sup>72</sup> described the successful use of aureomycin ointment in 3 cases of obstinate sycosis barbae.

Solomons<sup>196</sup> has found that sycosis barbae responds well to aureomycin ointment. He treated 22 cases, with cure in 1 week in 4, and in 2 weeks in 15. The 3 remaining cases had a few pustules until the end of the third week. No relapse has been observed in the regular post-treatment examinations. Eleven of 12 cases of folliculitis of other areas cleared up in 7 days to 3 weeks; only 1 showed resistance to treatment, but even in this case considerable improvement took place.

Viglioglia<sup>210</sup> believes that aureomycin ointment is the ideal medication for sycosis barbae and recommends oral aureomycin for all serious pyogenic skin infections, particularly those insensitive to classical forms of treatment.

## *Ulcer*

Hollander and Hardy<sup>89</sup> reported excellent results with aureomycin ointment in every one of 9 patients with phlebitis, dermatitis and ulceration, secondary to varicose veins.

Pfister<sup>158</sup> has described a case of large granulomatous ulcer of the face, which was at first thought to be malignant, but was later proved infectious. These granulomatous ulcers of the face and facial structures are associated with a high death rate. The ulcer involved the entire upper right maxillary region and was ex-



tremely tender. The finding of many dental abscesses suggested that they might be a possible source of infection. The patient, a mild diabetic, was well controlled by diet, and the infected teeth were removed. Postoperatively, treatment was carried on by daily injections of penicillin, in the outpatient department, where it was observed that the ulcerated area was becoming larger. Biopsy showed the lesion to be a chronic inflammatory one, and culture showed a coagulase-positive hemolytic *Staph. aureus*, resistant to penicillin but very sensitive to aureomycin and bacitracin. Treatment consisted of local cleansing and the systemic use of aureomycin and streptomycin. After the sixth day all cultures were sterile. By the eleventh day active healing was under way. Antibiotic treatment was discontinued on the fifteenth day, and the soft-tissue defect gradually closed, except for one small fistula in the region of the lacrimal sac. After discharge from the hospital, the patient was followed regularly, and the lesion went on to complete healing with barely noticeable scarring.

Viglioglia<sup>210</sup> used aureomycin ointment in 13 cases of varicose ulcer. All, without exception, improved. Eight ulcers healed completely in 1 or 2 months. In 2 cases, it was necessary to associate oral aureomycin on account of marked phlebitis.

Rutenburg, Schweinburg and Fine<sup>179</sup> found aureomycin of great value in the management of ulcerative or gangrenous lesions, in 7 of 10 patients with peripheral vascular disease. Four were diabetic, and most had signs of systemic infection and extending sepsis. All had failed to respond to penicillin, streptomycin or sulfonamides. Four patients were treated by local applications of a freshly prepared aureomycin solution (0.1%), 2 because of intolerance to oral administration, 2 because the infection appeared to be purely local.

In 1 case of *erosio interdigitale blastomycetica*, the lesions were completely healed in a week with aureomycin ointment.<sup>176</sup>

Logan and associates<sup>115</sup> obtained cure of infection, with intravenous and oral aureomycin, in 5 patients (4 diabetic) with leg

ulcers. Philip<sup>160</sup> reported similar results in 9 cases, using aureomycin ointment. Ludwig, Spier and Wolff<sup>123</sup> also had good results with aureomycin ointment in 5 cases of severe, extremely painful, chronic leg ulcer. Healing followed in 2 to 18 weeks.

Mallet-Guy and co-workers<sup>126</sup> reported the case of a woman suffering from a very painful sore on the lower lip. The lesion was so large that the mouth could not be closed, the left side of the face was swollen to the orbital border, and there was phlebitis of the facial veins. The patient was somnolent and her general state poor. Penicillin, sulfonamide, streptomycin, Percortin and X-ray therapy produced no change in her condition and the infection continued to spread. Paralysis of the left external oculomotor nerve developed. Spectacular response followed the addition of aureomycin, 4 days later, to the remedies already being used. By the next day, the patient was transformed and her fever had gone. *Staph. aureus* was cultured from the original site of infection and proved to be enormously resistant to penicillin. Six days after beginning aureomycin, the patient was almost well.

### *Veldt Sore (Tropical Ulcer)*

Ulcerations of the skin are frequent in the tropics and have widely varied etiologies. The commonest form, usually known as tropical ulcer, veldt sore, or phagedenic ulceration, is almost invariably associated with fusiform bacilli and spirochetes, which invade not only the surface area but also deep into the surrounding tissues. The preferred drugs have hitherto been the organic arsenicals.

Aureomycin is known to produce healing of tropical ulcers. Disappearance of the pus containing spirochetes and fusiform bacilli was observed within 48 hours, in 4 cases given aureomycin treatment.<sup>4,68</sup> Ampofo and Findlay<sup>5</sup> have reported equally rapid and complete healing in 8 cases. The organisms disappeared from the ulcers after 2 days' treatment with 750 mg. daily. There was no toxicity and no relapse.

Lasbrey<sup>107</sup> has reported the completely successful use of aureomycin ointment in 74 cases of tropical ulcer (sloughing phagedena) of the leg and nail-bed, in South African natives between the ages of 8 and 20 years. Swabs taken from the lesion showed, in the great majority of cases, Vincent's spirochetes and fusiform bacilli. Many ulcers contained additional organisms, including staphylococcus, streptococcus, and diphtheroids. All these patients were treated on an ambulatory basis. One chronic ulcer case, not included in the series, was hospitalized for a few days so that repeated swabs might be taken, and on it aureomycin also had a curative effect.

The treatment consisted of application of a thin layer of aureomycin ointment on dry gauze, after preliminary cleansing of the ulcer, and its retention in place with a small pad of cotton wool and a gauze bandage. In nail-bed ulcers, the necrotic remnant of the nail was left in place. The interval of several days between dressings made it impossible to determine the time at which organisms disappeared from the ulcer, but the disappearance of pain within 48 hours and the observation that at the first dressing, after about 5 days, the discharge was scanty and no longer offensive, and that the dressing was nonadherent and its removal painless, indicate that sterilization of the ulcer probably took place in about the same period as that noted by Ampofo and Findlay. Thirteen ulcers were epithelized within a week and 7 more within 2 weeks. Other cases stopped coming for treatment when the ulcer was about half healed. Not a single patient failed to show immediate response to aureomycin applications, including 3 with serologic evidence of syphilis. Lasbrey notes that either oral or local aureomycin treatment seems to produce approximately the same rate of healing.

Oral treatment has the advantage that the patient can continue treatment at home, keeping the ulcer covered with a clean dressing. This obviates the necessity for repeated visits, but topical therapy has the advantage of using much less of the antibiotic and thus rendering the treatment much cheaper.

Further studies by Ampofo and Findlay<sup>7</sup> on tropical ulcer indicated that when 3% aureomycin ointment was applied locally, healing was more rapid than with any form of oral antibiotic therapy, although the organisms themselves did not disappear so quickly from the lesion. In 12 children with ulceration of the lower limb treated with 3% aureomycin ointment, organisms disappeared from the smears after 3 to 5 days' treatment. Although no ulcer was of less than 4 weeks' duration and some were 3 or 4 cm. across, all were completely healed in 2 weeks or less, a rate of healing never before observed. They suggest that in addition to its antibiotic activity, aureomycin may also provide a growth factor deficient in the diseased tissues. The adequacy of tissue nutrition is a decisive factor in determining whether auto-inoculation of pus from a tropical ulcer may produce a new lesion. Inoculation over the fleshy part of the gastrocnemius muscle did not permit the development of a sore, but inoculation over the external malleolus gave rise to a rapidly spreading ulcer.

### *Verruca Vulgaris*

Reports on the value of aureomycin therapy for warts have been conflicting. It must be remembered that these lesions will often respond to suggestion alone. Coste and associates<sup>41</sup> believe that aureomycin therapy should be reserved for cases where the number of warts renders local treatment of each impractical, or where other attempts at general treatment have failed. They treated with success 1 case with more than 100 warts on the hands, in which most of the lesions disappeared in 45 days after administration of aureomycin by mouth.

### *Wounds*

Aureomycin is an effective aid to the surgeon in the treatment of wounds caused by accidental trauma and of infected operative wounds.

Logan and co-workers<sup>116</sup> have obtained immediate and effective control of infection by means of aureomycin, in 2 cases of human bites (q.v.) and in 2 cases of traumatic amputation of a lower extremity. One of the latter patients, whose wound was received in the upper third of the thigh, was in a very grave condition, with profuse foul drainage from the stump and a temperature of 104°F. 11 days after admission, despite treatment with penicillin and sulfadiazine. Aureomycin was given in addition, and the following day the temperature became normal for the first time. From then on, aureomycin was given alone and recovery was complete 6 weeks after admission. Similar success was reported by these authors in the prophylaxis and treatment of infection in several other cases of deep, lacerated wounds.

Using aureomycin Cole<sup>37</sup> obtained primary healing and restoration of motility, after immediate plastic tendon repair in a severe crushing injury to the hand, with gross contamination.

Marion and his colleagues<sup>128</sup> have reported the case of a patient with traumatic fracture of the pelvis, subepiphyseal fracture of the upper end of the right tibia, a right-sided bimalleolar fracture and a double fracture of the left tibia. This last injury was reduced satisfactorily and the reduction maintained by internal fixation, but in spite of all precautions, the knee became the site of an osteo-articular infection with *Staph. aureus*. After preparation with penicillin intra-articularly and intramuscularly, drainage of the knee-joint was provided by a wide internal-external arthrotomy. The temperature dropped temporarily but became spiking, with peaks each evening. Amputation appeared to be inevitable when aureomycin was begun by mouth, in the afternoon. The next morning, the temperature dropped, and on the following day returned permanently to normal limits. The local suppuration completely cleared up. These authors believe that aureomycin furnishes a very powerful weapon against the resistant strains of staphylococcus and of streptococcus which are unfortunately becoming more and more frequent.

In 21 cases undergoing emergency surgery for the repair of abdominal wounds caused by violence, and given aureomycin postoperatively to prevent peritonitis. Wright and Prigot<sup>218</sup> recorded very satisfactory results. There were 2 deaths, 1 from tension pneumothorax and 1 from hemothorax and shock.

Bablik<sup>10</sup> has successfully used aureomycin ointment for the treatment of postoperative dermatitis, in 4 patients undergoing radical mastoidectomy and in 3 who had a tracheal stoma following total extirpation of a malignant growth and X-ray treatment.

Clotting of a hemothorax, particularly when the clot has become infected, ordinarily demands protracted tube drainage and thoracoplasty, or extensive decortication of the lung. In such conditions, the combined use of VARIDASE\* Streptodornase-Streptokinase and aureomycin is of the greatest benefit. Carr and Robbins<sup>29</sup> have reported a case in which hemothorax infected with *Staph. aureus* developed after extrapleural pneumonectomy and first stage thoracoplasty, for bronchiectasis and multiple lung abscess. On 2 occasions injections were made of SK-SD and aureomycin, and at subsequent aspirations aureomycin was injected. All fibrinous material and clots were dissolved in 3 days, the temperature fell abruptly to normal, and aspiration was easily performed. Cure was completed by drainage and performance of the second stage of thoracoplasty.

De Bakey, in discussing the paper of Carr and Robbins,<sup>29</sup> himself reported a case of complicated hemothorax following multiple rib fracture. Fever developed, the pleural fluid was found to be purulent, and culture showed hemolytic *Staph. aureus*. Treatment consisted of injections of streptokinase and administration of aureomycin, since the organisms were resistant to penicillin. Recovery was rapid and the patient after leaving hospital had good respiratory function, although some pleural thickening remained at the right base posteriorly.

The complicated arrangement of the fascial planes and spaces of the hand make infected wounds in this region an occasion for

\*Reg. U. S. Pat. Off.

the exercise of the surgeon's utmost skill and care. Failure of accurate diagnosis and of suitable treatment, and particularly the premature use of antibiotic therapy alone, may lead to severe structural damage and loss of function of the hand. Mason and Allen<sup>129</sup> emphasize that the antibiotics do not relieve the surgeon of the responsibility for draining pus under tension, as in felon. Otherwise local necrosis may slowly develop without being suspected until too late. They illustrate this point by the case of a dentist who had injured his thumb with a dental drill about 3½ weeks previously. Several days after the injury, the thumb pulp became tender and painful and began to drain foul pus. The swelling was incised on 3 separate occasions and penicillin and aureomycin were given. At the time of his admission to hospital, pain and discharge had ceased, but the proximal phalanx and interphalangeal joint were diffusely red and swollen, and 3 tiny sinuses were draining an odorless pus. X-rays showed involvement of the phalangeal bone, and when adequate incision was made, a cavity was disclosed extending into the joint, the capsule of which was necrotic. A non-hemolytic streptococcus was found on culture. The involved part was splinted, and hot wet dressings applied for 2 days. Aureomycin was given for 3 weeks, combined with penicillin for the first week. The wound gradually healed and X-rays showed restoration of the bone. Motion of the joint was greatly impaired, a result which may be attributed to the fact that adequate drainage was not given until the infection had been present for nearly 3 weeks. While antibiotic administration was able to hold the infection in check to some extent, real improvement did not begin until free drainage had been established.

In a case of traumatic hemothorax reported by Monod and co-workers,<sup>141</sup> complete collapse of the lung and a quantity of fibrinous exudate was found at operation. Decortication and pneumolysis were performed and aspiration was continued. Following the operation the patient did well, and the lung expanded satisfactorily until the second day, at which time the drainage tubes became

plugged. An anterior pocket of fluid formed, which became infected with *B. proteus* in spite of antibiotic therapy. Aureomycin sterilized the effusion, and recovery followed.

The "crush" syndrome, first recognized as an entity in Great Britain at the beginning of World War II, consists of signs of progressive renal tubular damage following severe injury to large masses of muscle, such as may occur when the limbs have been compressed by heavy objects for several hours. If the patient can be carried over the period of oliguria or anuria, he may recover. Infection, whether carried in by the original injury, or arising from the invasion of devitalized muscle by pathogens already in the body, is encouraged by the presence of necrotic tissue and the lowered vitality of the patient. If this additional insult can be avoided, the patient's chances will obviously be better. Hoffinan and Schwartz<sup>87</sup> report recovery in 1 such case, in which aureomycin was used as the antibiotic agent.

## Yaws

In yaws treated with oral aureomycin, drying up of secondary lesions in about a week has been observed, with rapid healing but without alteration of the serologic reactions.<sup>4,68,116</sup>

Schaeffer, Loughlin and Joseph<sup>185</sup> examined the primary and secondary lesions of yaws in 20 patients undergoing aureomycin treatment. Using the phase contrast microscope, they were able to demonstrate morphological changes in the treponemata, beginning within 2 hours of the ingestion of a single dose of 2 or 5 Gm. and continuing for about 6 hours. The lesions dried up so rapidly that satisfactory scrapings were unobtainable in 14 cases at the end of 24 hours, while in the remainder only a few treponemata were visible, and these were abnormal in form. Twenty-four hours later, all lesions were apparently sterile.

Loughlin, Joseph and Schaeffer<sup>120</sup> studied the effects of aureomycin treatment in 30 West Indian patients with yaws. In this



group were included all stages of the infection, including "crab yaws," periostitis, bone gumma, arthritis, ulceration and gangosa. All of the cases were seropositive. It was found that in every case infectiousness could be stopped by a total dose of 10 Gm. of aureomycin. This amount also caused healing of the primary and secondary lesions and improved the tertiary ones. Systemic manifestations were entirely relieved within 48 hours.

Two dosage schedules were evolved, both of which gave equally good results. With either one dose of 2 Gm. daily for 5 days; or a dose of 5 Gm. on the first day, 3 Gm. on the second and 2 Gm. on the third, all treponemata were removed from the lesions within 48 hours. Primary lesions without ulceration or severe secondary infection were clean on the fourth day. When these complications were present, healing was slower, but clearing had begun by the third day and drying about the fifth day; healing was essentially complete in 14 to 30 days. Secondary lesions began to heal within 24 hours and healing was usually complete by the fifth or sixth day. Open wet lesions of the soles and palms were much improved by the fifth day but required about 14 days for complete healing.

Remarkable results were observed in several cases of far-advanced tertiary yaws, in which repair had seemed impossible and the outlook hopeless. In 3 cases with deep fungating chronic ulcers, oral dosage was increased and a capsule of aureomycin was opened and the powder sprinkled over the ulcer crater. Within a week, almost all the ulcers were completely healed. The authors quote one case of a young woman so deformed with yaws that she could stand only with the aid of a staff, and in a semi-crouched position. Two months later she walked almost erect without assistance. Another patient, who had been unable to sleep for almost 3 weeks before treatment, slept well after a single dose of 2 Gm. of aureomycin. The results obtained by these authors far exceeded those produced by doses of 300,000 units of penicillin repeated weekly for 3 or 4 weeks, and were at least equivalent to

those obtained by massive doses of penicillin. Since the report was submitted for publication, the authors have treated an additional 70 patients using the 5-day, 10-Gm. schedule. In the entire group of 100 patients, only 2 treated with the 3-day schedule presented infectious lesions which could be considered as relapses.

Lins, Nery Guimarães, Vasconcellos, and Lisboa Miranda<sup>112</sup> gave aureomycin to 1 child and 1 adult with yaws. The results were similar to those obtained with penicillin; that is to say, complete cicatrization in 15 to 16 days. The treponemata disappeared rapidly from the lesions. Allergic complications took somewhat longer to clear up, as is also true with penicillin. The authors believe that aureomycin is probably the ideal drug for the treatment of yaws.

Hill, Rhodes and Escoffery<sup>86</sup> have studied the efficacy of aureomycin in the treatment of yaws in 10 Jamaican children. Twenty-five mg. of aureomycin per kilo of body weight were given daily for 14 days. Six months after the beginning of treatment, all showed complete clinical cure, without relapse; 7 showed reversal or marked decrease in titer of the Kahn serological test, and 2 patients who were originally seronegative remained so. The authors feel that some significance may be attached to the fact that although these trials were carried on during the rainy season, when relapses appear to be most frequent in Jamaica, none occurred in this group of cases. The ultimate results of treatment appear to be the same as those obtained with penicillin, and aureomycin has the advantage of being effective when taken by mouth.

Ampofo and Findlay<sup>6</sup> found that an oral dose of 750 mg. of aureomycin daily sufficed to clear up the lesions of florid secondary yaws, and observed no recurrence during at least 6 months, in 5 cases. The action was less spectacular in late secondary and early tertiary yaws, but healing of skin ulcers and relief of the pain of periostitis were observed in 2 children. All of the 7 patients had positive Kahn reactions before treatment, but 1 had become negative and 1 doubtful 6 months later. The authors suggest that

longer courses might have even greater influence on the serology, making aureomycin superior to penicillin in this respect, and note that aureomycin will greatly simplify the problem of eliminating yaws from infected communities.

## CHAPTER SEVEN

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INFECTIONS PRIMARILY INVOLVING  
THE EYE

AN 0.5% solution of aureomycin borate is essentially non-irritating to the conjunctiva,<sup>11</sup> so that the antibiotic may be used locally, as well as by a combined systemic and local approach.

Ainslie<sup>4</sup> has found no serious toxic effects from the systemic administration of aureomycin in eye disease. For local administration, he finds the ointment to be the most effective preparation, since it is so convenient to use and its antibiotic activity is so high. Aureomycin drops (0.5%) are valuable in superficial infections and may be given at frequent intervals without harmful effects. Ainslie has not seen any instance of corneal excoriation, even when instillations are given very close together—for example, every minute for an hour or more. Marr<sup>58</sup> and co-workers state that aureomycin in ordinary therapeutic concentrations does not delay the healing of corneal defects.

Aureomycin when given locally does not penetrate the intact normal corneal epithelium, but does so when the epithelium is abraded or infected. After passing the blood-aqueous barrier, systemically administered aureomycin remains longer in the ocular tissues and fluids than do other antibiotics.<sup>31</sup> Garcia Nocito and associates<sup>40</sup> state that when aureomycin is given intravenously, it appears in large quantities in the cornea, iris, and ciliary body. The activity of aureomycin is not impaired by the addition of argyrol,

pilocarpine, scopolamine, dionine or epinephrine to the ophthalmic solution.<sup>64</sup>

## *Blepharitis*

Ainslie<sup>2,3</sup> considers blepharitis to be one of the most distressing afflictions seen by the ophthalmologist. It may be caused by a wide variety of pyogenic organisms, of which by far the most common is *Staph. aureus*. Most cases can be cured by suitable remedies, if treated before the disease becomes chronic, but some may be very obstinate and painful. He has treated 30 consecutive cases, in which the infection had been present for 3 months to more than 20 years and had failed to respond to numerous forms of treatment. Encouraging results were obtained with aureomycin, but cures lasting 3 months or more were possible in only two-thirds of the cases, a fact which emphasizes the importance of proper treatment in the early stage.

Of 18 cases of blepharitis due to *Staph. aureus*, and insensitive to penicillin and sulfonamides both clinically and *in vitro*, Ainslie obtained cure in 10. No recurrence took place in the following 6 months. Five others were cleared up but recurrences necessitated further treatment. Aureomycin was successful in clearing up 2 cases of blepharoconjunctivitis caused by the Friedländer bacillus. Four of the apparently cured cases had suffered from infection of the lids for 6 to 26 years. One patient with *H. influenzae* blepharitis of 6 years' duration cleared completely in 12 days of aureomycin administration, and another who had suffered from *Staph. aureus* blepharitis for 26 years, with only brief intervals of improvement in spite of a wide variety of treatments, was also cured in 12 days.

Bellows, Richardson and Farmer<sup>11</sup> have reported that a child with severe recurrent hordeola, treated unsuccessfully for many weeks with penicillin and the sulfonamides, completely recovered after 5 days of local and systemic aureomycin therapy.

Garcia Nocito and co-workers<sup>40</sup> obtained great improvement

in 3 cases of chronic blepharoconjunctivitis; and in 27 cases of conjunctivitis of severity ranging from hyperacute to chronic, there was great improvement or cure in 23, and only 4 comparative or complete failures. Aureomycin drops were instilled hourly as the sole medication. Improvement was observed usually within 24 hours and, in most cases, cure in not more than 48 hours. Relapse was observed in only 1 case.

The etiologic agent of dandruff, *Pityrosporum ovale*, is an important factor in the causation of blepharitis. It is usually necessary, when dandruff is present, to direct treatment towards its cure, otherwise relapse may be expected after aureomycin treatment of the blepharitis. Hickey<sup>43</sup> recommends frequent shampoos, the use of mercury ointments and later of a vitamin A ointment, and vitamin A by mouth.

Fraser<sup>39</sup> states that aureomycin ophthalmic drops given twice daily for 1 month produced such great improvement in a case of extremely chronic ulcerative blepharitis that the patient's outlook on life was completely changed. In 5 years, he had had only 1 remission of the condition, in spite of the use of all recognized forms of treatment.

Vaccinia of the eye following smallpox vaccination is infrequent, but may produce scarring and in about one-third of the cases involves the cornea, with attendant danger of loss of vision. King and Robie<sup>51</sup> report 1 case, without corneal involvement, in a two-year-old boy. Aureomycin (250 mg. every 8 hours) was given for 96 hours, together with borate eye drops 4 times daily for 7 days. Intramuscular penicillin, 100,000 units, was given twice daily for 5 days, and local wet compresses of 1:100,000 potassium permanganate solution were used for half an hour 4 times a day. Vitamin C, 50 mg. twice daily, was given by mouth. Within 24 hours, very marked improvement was observed. The lesions on the eyelids became stationary and the edema began to decrease. No extension to the conjunctiva or cornea took place, and the condition had almost disappeared within 72 hours.

## Conjunctivitis

Local application of aureomycin has been used with good results in the intractable conjunctivitis associated with long-established leprosy;<sup>37</sup> the ocular involvement seen in erythema multiforme;<sup>68</sup> and the conjunctivitis produced by the virus of Newcastle disease.<sup>81</sup>

Badia<sup>8</sup> states that in a number of subacute cases of conjunctivitis, in which other medication had not been effective, aureomycin brought about evident improvement within 48 to 60 hours. In chronic cases of conjunctivitis which had resisted all previous therapy, Garcia Nocito and his co-workers<sup>40</sup> found that improvement usually took place within 76 hours.

*Bacterial*—Pritikin and co-workers<sup>70</sup> have reported uniformly gratifying results following the local instillation of aureomycin drops, in 16 cases of acute or chronic conjunctivitis treated by them. They found that improvement set in within 24 hours and cure was usually complete in 3 days. The organisms present included *Staph. aureus*, *C. xerosis*, *Staph. hemolyticus*, *Staph. nonhemolyticus*, *D. pneumoniae*, *Strep. hemolyticus*, and fusiform bacilli. The authors emphasize the necessity for eradication of any nidus of infection elsewhere, which may be responsible for conjunctival infection and which may serve to perpetuate it.

As a rule, the mucopurulent conjunctivitis of infants responds promptly to the usual antibacterial remedies, but Ainslie<sup>4</sup> observed 8 cases which had failed to respond to treatment, including penicillin in 5 cases. After 12 hours of local aureomycin instillation, striking improvement was obvious and the condition was cured within 3 or 4 days. One adult with a similar condition, the cultures from the eye yielding nothing but a few colonies of *Staph. albus*, received no benefit from penicillin but was cured in 2 days with aureomycin.

Garcia Nocito and co-workers<sup>40</sup> treated 35 cases of conjunctivitis, acute, subacute and chronic, with aureomycin drops. Aureomycin was given over a period of 24 to 76 hours. Twenty-one

cases were cured, 5 much improved, 3 slightly improved or unimproved. Complete cure was not obtained in the 6 chronic cases, but 4 were much improved.

Very satisfactory results were obtained by Bellows, Richardson and Farmer,<sup>11</sup> in a number of cases of conjunctivitis caused by staphylococci. Five cases of acute conjunctivitis cleared up in 3 to 6 days. One case of subacute conjunctivitis with corneal infiltration improved dramatically within 2 days. One case of chronic conjunctivitis with corneal infiltration improved after 1 week of aureomycin instillations. In only 3 cases out of 14 was aureomycin ineffective; 1 chronic blepharitis, 1 chronic conjunctivitis, and 1 acute conjunctivitis.

Braley and Sanders<sup>22</sup> treated 56 cases of staphylococcal conjunctivitis. The infection was often a mixed one, and the conjunctivitis was usually accompanied by blepharitis, and often by superficial punctate keratitis. Most of the patients were cured within the first 12 to 24 hours. Remarkable relief was commonly experienced within a few hours, although a number of the patients had suffered from recurrent conjunctivitis for many years. When treatment was continued for only 24 to 48 hours, there were some recurrences, the number of these decreasing as the length of treatment was increased. Recovery occurred in less than 24 hours, without recurrence, in 4 cases of influenzal conjunctivitis. Similar results were obtained in 5 patients with pneumococcal conjunctivitis after 16 hours of treatment, and there were no recurrences.

Ainslie<sup>4</sup> has successfully treated a number of cases of conjunctivitis caused by penicillin-resistant *Staph. aureus*.

Hickey<sup>44</sup> reported cure in 1 severe case of mixed staphylococcal and streptococcal conjunctivitis, with marked systemic disturbance. The patient felt well 24 hours after beginning the use of aureomycin eye drops, and the eyes were almost normal after 48 hours.

In 7 cases of mixed infection of the eye, treated with aureomycin by Bellows and associates,<sup>11</sup> *Staph. albus* was constantly

present, and the infections were complicated by *S. viridans*, *Ps. aeruginosa*, hemolytic streptococci, *B. subtilis*, a diphtheroid and an unidentified Gram-negative rod. No improvement was noted in 3 cases: a case of acute conjunctivitis due to *S. viridans* and *Staph. albus*; a case of chronic conjunctivitis with *Ps. aeruginosa* and *Staph. albus*; and a case of acute conjunctivitis due to *B. subtilis*, *Staph. albus* and a diphtheroid. The 4 others were improved or cured.

McWilliam and Wilson<sup>59</sup> have found local aureomycin useful in pneumococcal conjunctivitis and other bacterial infections of the eye. In 1 case of recurrent pneumococcal conjunctivitis, not responding to treatment over a 10-year period, rapid resolution resulted. All cultures after the first one were negative. They believe that aureomycin may be very helpful against penicillin-resistant organisms and in cases of chronic conjunctivitis not responding to therapy.

Braley and Sanders<sup>22</sup> have reported the successful use of aureomycin locally in 10 cases of pneumococcal conjunctivitis. All were cured without recurrence.

In 1 patient with acute *H. influenzae* conjunctivitis, treated by Braley and Sanders,<sup>22</sup> recovery was complete and cultures were negative within 3 days. Duke-Elder and associates<sup>36</sup> also reported good response in a case of *H. influenzae* conjunctivitis.

The Koch-Weeks bacillus is now believed to be identical with *H. influenzae*. Raïs<sup>72</sup> has obtained cure following topical aureomycin treatment in 3 cases of Koch-Weeks conjunctivitis, and Caruana and Hamza<sup>24</sup> found aureomycin to be superior to streptomycin or to conventional methods in a series of 100 childhood cases.

Of 2 cases of acute *Ps. aeruginosa* conjunctivitis, treated with aureomycin by Bellows and co-workers,<sup>11</sup> 1 showed no improvement at the end of 3 days; but in the other, in which there was severe corneal involvement, infection was halted by the use of aureomycin instillations, together with delimiting keratotomy.

Local use of aureomycin borate solution produced prompt

response in 1 case of meningococcal conjunctivitis and in 1 case of *E. coli* conjunctivitis, reported by Braley and Sanders.<sup>21</sup> Aureomycin appears to be the most effective remedy available for use against the diplobacillus of Morax-Axenfeld. Nine cases were treated by these authors: 5 were relieved, and the conjunctiva freed from bacteria; 1 patient had a recurrence after treatment was stopped; in 3 cases no definite improvement was observed.

*Viral*—Ainslie<sup>2</sup> believes that aureomycin is particularly effective in those cases of conjunctivitis (presumably of virus origin) from which no organism can be cultured.

Herpes zoster ophthalmicus is primarily an expression of neurologic rather than ophthalmologic involvement, and its response to aureomycin is discussed in the chapter, "Infections of the Central Nervous System." It may here be briefly noted that the pain, edema and local eye lesions subside with great rapidity on oral administration of aureomycin, and corneal ulcerations heal.<sup>7,8,17,48,52</sup>

Aureomycin has produced excellent response in follicular conjunctivitis, often stated to be a self-limiting disease. In 11 cases treated by Ainslie,<sup>2,4</sup> the self-limiting property was not very evident, since the disease had continued in spite of numerous treatments for 4 to 7 weeks, and in 2 cases, there was superficial vascularization surrounding the cornea. In 1 case, severe corneal ulcer was present. While in the first 2 cases aureomycin was given orally as well as locally, the improvement in every case was so rapid and apparently permanent that the author believes that local administration alone is sufficient. Two chronic cases of conjunctivitis also responded well even though the condition had been present for years, but in these cases there was some tendency toward relapse.

In an epidemic of acute follicular conjunctivitis, occurring in Hawaii in the first half of 1951, Holmes<sup>47</sup> observed that local applications of sulfonamides and various antibiotics were effective, but that the most dramatic cure was obtained with aureomycin or 30% sulfacetimide. Oral antibiotic administration was found valuable, as a supplement to local treatment, in stubborn cases. The



epidemic was of viral origin but did not appear to be related to epidemic keratoconjunctivitis.

Braley and Sanders<sup>21</sup> observed prompt response to aureomycin borate solution locally in 6 cases of inclusion conjunctivitis, most of them in newborn infants who had suffered from the disease for 5 days to 2 weeks. Purulent discharge ceased within 24 hours and the conjunctiva returned to normal in 3 days to 1 week. No inclusion bodies could be demonstrated from conjunctival scrapings after 24 hours of aureomycin treatment.

Charbonneau<sup>25</sup> has reported a patient recovering very slowly from pemphigus, in whom after 1 year there remained a blepharokeratoconjunctivitis which was not touched by ordinary therapy. Instillations of aureomycin into the eyes brought cure within 48 hours.

Mercier<sup>61</sup> reported the successful treatment with aureomycin drops of a young soldier with signs of old trachoma and a recent keratoconjunctivitis. Other medications had failed but the condition, whether caused by a relapse of the trachoma or a secondary infection, rapidly responded to aureomycin.

Braley and Sanders<sup>21</sup> were unable to find a specific response to aureomycin instillations in 8 cases of vernal conjunctivitis. Two patients showed disappearance of the membrane and some relief of symptoms, but this improvement appeared to result from action on secondary invaders. One patient with atypical vernal conjunctivitis had also a large central corneal ulcer, of undetermined origin. This ulcer healed promptly under aureomycin therapy. While aureomycin was being given, itching and discharge decreased, but returned when treatment was discontinued. Legrand<sup>53</sup> claims to have relieved some cases by the use of aureomycin drops.

Brügger<sup>23</sup> has used aureomycin successfully in a case of phlyctenular keratoconjunctivitis in a four-year-old girl, with blepharospasm and photophobia. The child also had tuberculous mediastinal lymph nodes, with pulmonary infiltration and tuberculous empyema. The ocular manifestations responded promptly to the

application of 1% aureomycin ointment. No blepharospasm or photophobia remained after 1 week. Because of the effectiveness and simplicity of aureomycin administration, the author considers it to be indicated in all such cases.

## *Corneal Infection*

Garcia Nocito and co-workers<sup>40</sup> have reported cure in 14 out of 15 patients with corneal infections, including herpetic keratitis, marginal ulcer, central ulcer, extensive ulceration with hypopyon, catarrhal ulceration, keratitis punctata.

A very severe form of corneal ulceration is produced by infection with *B. pyocyaneus*, virtual or complete loss of the eye frequently occurring within a day or so of admission. Most strains of the organism are sensitive to streptomycin, but Bignell<sup>13</sup> has described a case resistant to streptomycin but sensitive to aureomycin; the ulcer healed, leaving lessened but useful vision, after local treatment with streptomycin and aureomycin.

Wilson<sup>88</sup> has reported a case of bilateral sclerosing keratitis in which, after prolonged and varied treatment, including the use of aureomycin locally and orally, only partial recovery had been obtained. When the patient was found to react strongly to staphylococcus toxoid, she was desensitized to it, after which improvement was steady. Final vision was 20/20 in each eye.

Berliner<sup>12</sup> states that aureomycin has replaced other drugs as the treatment of choice for ulcerative keratitis. One drop of 0.5% solution instilled into the conjunctival sac every hour or 2 throughout the day brings rapid relief of symptoms and re-epithelization. The length of treatment required is directly proportional to the size of the ulcer.

Johnstone<sup>49</sup> has reported 2 cases of filamentary keratitis which cleared up promptly with aureomycin drops. One patient had suffered from keratitis for 8 years and had undergone every conceivable variety of treatment.

*Episcleritis*—No improvement was observed in 1 patient with episcleritis, who was given local aureomycin therapy by Bellows and co-workers,<sup>11</sup> but complete recovery followed within 2 days in another patient treated systemically with aureomycin, 50 mg. 4 times daily. This difference in results is understandable, since episcleritis is believed to be merely a local evidence of some systemic disease.

*Herpes Simplex Corneae*—All herpetic lesions of the eye and skin, excluding those of zoster, are at present believed to be due to the virus of herpes simplex. The corneal ulceration caused by this virus may result in severe permanent scarring. Aureomycin appears to be to some extent virucidal.<sup>20</sup>

Recurrent herpes simplex corneae yields to aureomycin either in ointment or solution form, the ulcer healing in 24 to 48 hours, with immediate relief of pain.<sup>19,67</sup>

Duke-Elder and co-workers<sup>38</sup> have reported aureomycin to be totally ineffective in herpes simplex corneae. On the other hand, Zeller<sup>89</sup> found it effective in all of his series of 7 cases, healing occurring in 4 to 21 days.

Aureomycin treatment is effective in about 2 out of 3 persons with dendritic ulcers of the cornea, or with superficial keratitis due to the same virus, with involvement of either the epithelium or the stroma, or both.<sup>20,82</sup> Thygeson and Hogan<sup>82</sup> suggest that variation in virulence may account for many of the failures.

Braley and Sanders<sup>21</sup> reported prompt benefit from aureomycin borate drops in 13 of 21 cases of dendritic keratitis with early involvement of the stroma. Ulceration was healed in 24 hours; the infiltrate ceased to spread and in most cases disappeared altogether. In 1 case in which the ulcer involved about two-thirds of the cornea and had resisted all therapy for about 4 years, arrest of the disease was obtained with aureomycin, by Appelman and Hale.<sup>6</sup> Reuling<sup>74</sup> reported symptomatic improvement within 36 hours in 3 stubborn cases, and healing after 4, 7 and 10 days.

Henricson<sup>42</sup> has used aureomycin solution in 7 cases of herpetic

keratitis, 3 cases of dendritic keratitis and 1 case of keratitis superficialis punctata. Results were most striking in acute conditions and in patients whose corneal changes were at an early stage. The 3 acute cases of herpetic keratitis were all cured, as were 2 of the 4 chronic cases; 1 chronic case was improved and 1 unchanged. All of the cases of dendritic keratitis were cured, including 1 chronic case. Three to 5 days were usually sufficient for complete recovery. Pain disappeared in the first 2 days, and there were no exacerbations. Improvement was observed in the case of superficial punctate keratitis, but was only slight.

The case of a man who had lost one eye in the first World War, and who developed dendritic keratitis in the remaining eye, has been reported by Hartmann and Forest.<sup>41</sup> After surgical abrasion of the cornea, 0.5% aureomycin solution was instilled every hour during the day and every 2 hours at night, for the first 24 hours; after that a 2.5% solution was used. (A 5% solution was tried for 2 doses but found to be too irritating). After 3 days of treatment, the cornea no longer retained fluorescein. Biomicroscopic examination, 1 month after the beginning of aureomycin treatment, showed no scar tissue, and the patient's vision was 10/10.

*Disciform Keratitis*—Disciform keratitis, which may be caused by the virus of herpes simplex, appears in association with such virus infections as mumps, chickenpox, and influenza, and is treated in the same way as dendritic keratitis. Müller-Stüler<sup>64</sup> feels that, in view of the limited therapeutic possibilities in disciform keratitis, the following case is worthy of mention. The patient was a fourteen-year-old girl, who had suffered for 6 weeks with severe disciform keratitis of the right eye. Aureomycin drops were instilled every half hour, and within 3 days the infiltration was clearly regressing. The cornea was abraded on several occasions to permit better absorption of the aureomycin. Within a week, the ring-like peripheral opacities had cleared up. The rate of healing became slower after 2 weeks of treatment, and aureomycin solution was therefore injected subconjunctivally. This was followed by some

chemosis and slight scleral congestion. However, these disappeared within a week. Healing, except for a corneal scar which was half the size of the original lesion, was complete in 5 weeks. Toward the end of treatment, a very small abscess appeared in the center of the previous area of infiltration, but cleared following treatment with aureomycin and penicillin drops. Vision without glasses was 6/8.

Four cases of disciform keratitis were treated with aureomycin by Ainslie;<sup>4</sup> 2 of them received only topical applications, and did not respond; 2 were given aureomycin by subconjunctival injection and improved rapidly. The corneal infiltration cleared until the eye became entirely quiet.

Joseph<sup>50</sup> also observed a good response in a case of disciform keratitis, little remaining after 4 weeks but a fairly dense central opacity. The method of administration of aureomycin in this case was subconjunctival injection.

Barnes<sup>9</sup> found topical aureomycin borate solution to be effective in 3 cases of disciform keratitis, controlling the infection within 7 to 13 days. He believes, however, that effective atropinization is still necessary.

*Epidemic Keratoconjunctivitis* (Punctate Keratitis, "Shipyard Conjunctivitis")—Aureomycin is effective against epidemic keratoconjunctivitis but does not affect the corneal infiltrates.<sup>35,46</sup> As a rule, corneal involvement in this infection slowly clears up spontaneously, and the prognosis for vision is good.

If recognized early, epidemic keratoconjunctivitis responds very satisfactorily to treatment. Corr  ard and Plessier<sup>27</sup> state that there are 3 effective lines of treatment: convalescent serum, aureomycin and shock therapy. Serum, if given early and in large doses, can ward off keratitis, but is difficult to obtain and is ineffective against the conjunctivitis. Shock therapy is reserved for occasions when aureomycin or serum is unavailable.

Braley and Sanders<sup>21</sup> found favorable response to aureomycin instillations in 25 of 53 patients, but stress that it must be used

before corneal opacities appear, preferably before the fifth day of the disease, and continued for at least a week or 10 days. They recommend instilling aureomycin solution into the conjunctival sac every  $\frac{1}{2}$  to 1 hour.

Braley<sup>18</sup> used aureomycin in the treatment of 51 patients with epidemic keratoconjunctivitis. In 23 patients whose treatment was begun early, the duration of the disease was shortened and the number of corneal opacities reduced. Patients treated late received no benefit.

Bellows and his colleagues<sup>11</sup> have reported on 7 cases of epidemic keratoconjunctivitis treated with aureomycin; in 5 acute cases, recovery took place in 6 to 10 days. In 1 subacute case with many corneal opacities, recovery occurred in 1 week. In a seventh case, first seen 5 weeks after onset, and not responding to other remedies, dramatic response was noted 24 hours after beginning aureomycin treatment. Recovery was complete in 4 days.

Ainslie<sup>2</sup> has reported control within 3 days in a severe case of keratoconjunctivitis, apparently of vaccinal origin, in which corneal and lid ulceration developed 10 days after vaccination. Secondary infection by *Strep. viridans*, *Staph. albus* and *B. xerosis* was present. After 36 hours of aureomycin instillations, both ulcers had almost completely vanished. Mercier<sup>60</sup> obtained satisfactory results in 5 cases.

*Mooren's Ulcer*—Mooren's ulcer, or rodent ulcer of the cornea, is a chronic ulcer with marginal undermining which occurs usually in elderly people. Ulceration begins at the border of the cornea and slowly extends over its surface. The etiology is unknown. Braley and Sanders<sup>22</sup> reported definite benefit from aureomycin in 2 patients with the Mooren type of ulcer.

Mercier<sup>61</sup> has used aureomycin in a number of cases of eye infection in which penicillin had given poor results. One such case was that of a marginal corneal ulceration of the Mooren type, which was extremely painful. Prompt relief of pain and healing of the ulcer resulted from a few days of aureomycin instillation.

## *Periorbital Infection*

Chronic or acute recurrent inflammation of the orbital socket may be a source of great discomfort and inconvenience to patients who have lost an eye. Macivor<sup>57</sup> believes that the infection is due in large part to improper hygiene, particularly in the handling of the prosthesis. Conjunctival tags in the orbital socket may provide deep crypts suitable for bacterial multiplication; and these must be removed before the infection can respond. He has found aureomycin hydrochloride particularly useful in the treatment of *Proteus vulgaris* and *E. coli* infections of the eye socket, and employed it successfully in 1 infection by *E. coli*, 2 by pneumococcus, 1 by *H. influenzae* and 1 by *Proteus vulgaris*. In 120 cases of orbital inflammation, he found 8 cases of allergy to the plastic of the prosthesis. Improvement occurred within 4 days in 1 case of infected anophthalmos, treated with aureomycin by Bellows and associates;<sup>11</sup> the profuse discharge from the orbit decreased to negligible proportions.

## *Trachoma*

Trachoma has been described as the most terrible and most tenacious scourge ever known to the human race.<sup>79</sup> Sakon<sup>76</sup> speaks of it as having a greater number of victims than any other disease in the world. Although its history dates back about 35 centuries, there is perhaps no other disease in all medicine whose etiology, pathology, and treatment are more obscure.<sup>1</sup>

Physicians accustomed to seeing and treating large numbers of patients with trachoma have reported greater improvement in shorter time, following the use of aureomycin, than with any previous method of treatment.<sup>4,15,16,63,73</sup> They have seen prompt relief of discomfort and discharge, reduction of papillary hypertrophy, and regression of the pannus. In many cases, actual cure has been claimed.<sup>15,32,36,73</sup> Even trachoma of many years' standing

has been greatly benefited.<sup>11,22</sup> Both oral and local therapy has been successful, and Boase<sup>15</sup> found evidence that resolution progresses after treatment. He believes that some patients listed as "improved" may, after discharge, go on to cure. Ainslie<sup>4</sup> also observed progressive improvement after treatment had been finished.

With the older classical forms of treatment, treatment might have to be continued for 1 to 6 years or longer, and cure was uncertain.<sup>15</sup> Aureomycin produces marked improvement in a short time, with striking symptomatic relief even in the most chronic cases.<sup>2</sup>

It was inevitable that some disagreement should arise as to the cause of the beneficial effects seen in aureomycin-treated trachoma. Some believe that the action of aureomycin is truly antiviral, while others claim that it is effective only through its action on secondary infection.<sup>30</sup>

Desvignes and Morault,<sup>33</sup> who were among the first to report the favorable action of aureomycin in trachoma, have surveyed the reports of other authors on this subject. Their own experience would indicate that aureomycin has a specific action on the trachoma virus, and they believe that, even if it does not bring about definitive cure, it is the best remedy obtainable. Most of the cases which they themselves have seen in Paris have been old cases, but by chance they were able to observe 1 case near its beginning. Apparently permanent cure followed the use of aureomycin.

Poleff and Viennot-Bourgin<sup>69</sup> believe that they have evidence of a true virucidal action of aureomycin in experimental trachoma. They produced trachoma experimentally in the healthy conjunctiva of a man blind from incurable optic atrophy. Treatment with the classic antibiotics (penicillin and streptomycin) alone was absolutely without influence, while aureomycin, applied later in the disease but still during the active stage, showed itself to be distinctly effective. The use of a sulfonamide ointment in high concentration was without effect until the classical mechanical methods



were also employed. However, even under these conditions, local sulfonamide therapy was unable to prevent relapse. Aureomycin hastened definite cure.

d'Andrade and Breda<sup>29</sup> studied 6 patients with trachoma, who were given oral aureomycin, as well as local applications of aureomycin solution. They concluded that aureomycin did not cure the virus infection, but was useful against the associated secondary invaders, and stated that they had seen no case in which the histologic picture of trachoma had disappeared under aureomycin treatment.

On the other hand, Raïs and Arroyo<sup>73</sup> used aureomycin in about 20 cases of trachoma, without apparent associated infection and in all stages of the disease. Within 24 to 48 hours, all functional signs had disappeared, no matter what the degree of severity of the trachoma, and at the same time the congestion of the bulbar conjunctiva disappeared. They confirmed Boase's observation as to the rapid disappearance of the trachomatous pannus, and found the cornea to be clear within a week on the average. No other antitrachoma treatment had, to their knowledge, such a definite and certain effect on this serious complication.

In order to rule out every possibility that a favorable response to aureomycin in trachoma was due to an action on secondary bacterial infection, Ngo-Van-Hieu<sup>66</sup> selected for treatment cases without evidence of such complication. In the first, second and third stages of trachoma, local application of aureomycin controlled the disease in 1 week and brought about complete or nearly complete healing in 2 or 3 weeks. Almost equally good results were seen in trachoma IV. Arrest of the disease was noted in trachoma V, but aureomycin had no influence on the pannus or the palpebral complications. The ulcerated pannus became scarred and remained opaque, after 3 or 4 weeks of treatment. No effect on the xerosis of trachoma VI was seen at the end of a month of treatment. The author feels that a combination of aureomycin treatment with surgical treatment (careful curettage followed by massage; subcon-

junctival injections of mercury cyanide) gave better results than medical treatment alone.

Lyons<sup>56</sup> stresses that however great an immediate improvement is produced by any remedy, it cannot be considered evidence of cure unless it is followed by disappearance of the follicles and acceleration of healing. This does not appear to be the case with the sulfonamides. Another criterion of cure would be the loss of infectivity following treatment. He found that 2 trachomatous children, of 3 treated with sulfanilamide, were still infectious and the third child was possibly so. In contrast, the patients appeared to be no longer infectious after treatment with aureomycin. Clinically, the response to aureomycin was superior to that following other forms of treatment, but the results in Egypt were less spectacular than those claimed in other countries. He points out that in Egypt, trachoma is usually heavily complicated by other bacterial infections and takes, as a rule, an insidious mild course, beginning in infancy and causing little disability until the late stages are reached.

Trope,<sup>84,85</sup> of South Africa, found that for the outpatient treatment of trachoma, a suspension of aureomycin hydrochloride in castor oil was more stable and no more irritating than the aqueous solution of aureomycin borate. The oily suspension of aureomycin was used in 47 cases. These included 17 cases of trachoma and 30 cases of inflammatory eye conditions of uncertain origin, involving the conjunctiva or cornea, or both. The results were dramatic in all stages of trachoma, doubtful in 3 cases of iridocyclitis and good in all the other cases (8, acute conjunctivitis; 1, follicular conjunctivitis; 3, blepharitis; 5, corneal ulcer; 2, corneal laceration; 1, dendritic ulcer; 1, hypopyon; 3, superficial punctate keratitis; 1, herpes corneae; 1, acute marginal vascular keratitis; 1, disciform keratitis). The great advantages of this vehicle for dispensing aureomycin are its simplicity and economy, the persistence of antibiotic activity and the fact that it permits treatment at home. Aureomycin used in this way renders practicable the treatment of

trachoma by mobile units in areas at great distances from hospitals.

While trachoma is fortunately of little epidemiologic or public health importance in the United States and Canada, in many other parts of the world it is a very serious problem. Sakon and associates<sup>75</sup> state that in the southern part of Morocco, 90 per cent of the population suffer from trachoma. In the face of this enormous mass of infection, in a backward, undernourished population ignorant of the gravity of the disease, it is understandable that the African physician is interested in any new and promising therapeutic weapon, since the results of sulfonamide therapy have been disappointing. The authors accordingly undertook the study of the newer antibiotics, including aureomycin, in a very thorough manner. The patients were hospitalized, in fairly strict isolation, and great attention was paid to their nutrition, 4 meals a day plus polyvitamin therapy being given. Regular observation was undertaken by qualified medical personnel, including frequent examinations by means of the corneal microscope. Disappearance of inflammation and striking reduction in the hypertrophic condition of the conjunctiva were seen in every case; as well as decrease in the number of follicles and improvement in their appearance. In early trachoma, the follicles disappeared more or less completely, leaving fine scars. In florid trachoma, scarring was hastened and the follicles became less prominent. No effect upon pannus was observed. The authors feel that aureomycin is a valuable auxiliary to classical treatment, and has the important advantage of being harmless to use and well tolerated. In addition, an effective course of aureomycin is much shorter and less painful than the standard treatment. Both drops and ointment appear to be equally effective.

Hingerty and Lavery<sup>45</sup> found that a suspension of aureomycin in plasma maintained its activity almost unimpaired for 4 weeks, and used it in 2 cases of trachoma, with satisfactory results.

Clinical studies by Ahmad<sup>1</sup> led him to consider aureomycin an excellent therapeutic agent for the treatment of trachoma. Relief of distressing symptoms usually occurred in 3 or 4 days, and local

lesions such as congestion and early follicles disappeared, as did scleral and corneal inflammation. Aureomycin was used locally, as eye drops or ophthalmic ointment, or by painting the lids with eye lotion; or was given orally in a daily dose of 1 Gm. In a series of 64 patients treated by Ahmiad with 1 or several of these methods, 65 per cent of the patients were clinically cured, 24 per cent were improved (contact was lost with 5 of these patients) and 11 per cent were either not relieved or discontinued treatment. Keratitis and scleritis rapidly improved. Most of the cures occurred in early cases of stage I and II. The period of post-treatment observation has in some cases extended for more than a year.

Moutinho and co-workers<sup>62</sup> have treated 40 cases of trachoma, using an anhydrous neutral ointment especially prepared for them which contained 25 mg. of aureomycin in 5 Gm. of ointment. This preparation they have found very active and very well tolerated. Of 28 cases treated in stage I or II, 19 were much improved or clinically cured; of 11 patients in stages III and IV, 8 were very much improved or clinically cured. In most cases, follicular hypertrophy decreased, inclusion bodies disappeared from scrapings in a few days, and pannus was favorably influenced. Some of these patients had trachomatous keratitis or corneal ulcers, and these also healed rapidly.

According to Pullar,<sup>71</sup> trachoma as seen in Kenya, East Africa, is relatively mild and is more of a nuisance than a crippling disability. He has tried various methods of handling the infection and found that, with penicillin, results were very disappointing, the antibiotic appearing to affect only secondary infection. Somewhat more encouraging was the outcome of treatment with a combination of local and oral sulfonamide administration, expression of the follicles, and the use of penicillin drops for secondary conjunctivitis. However, Pullar found aureomycin ointment to be the most promising medication yet tried. In nearly every case there was marked improvement in the symptoms, and few relapses were observed.

In 15 cases of trachoma treated by Henricson,<sup>42</sup> 12 of them chronic, and 9 of them having granules, the effect of aureomycin was good. Cure followed in 10 cases, improvement in 4, and failure in 1. Healing was more rapid than is usually seen with other methods of treatment, and the response was particularly good in acute cases. Results were less satisfactory in 2 cases, in which treatment had been discontinued rather early on account of the impatience of the patient. Under the slit lamp, trachoma granules were observed to begin shrinking soon after the beginning of treatment, and to disappear entirely after 6 days. All of the 15 patients expressed satisfaction.

Ainslie<sup>4</sup> has reported, in 7 patients with stage II trachoma passing into early stage III, remarkably good response to aureomycin drops and ointment, and in 3 of these cases to systemic aureomycin as well. These cases showed highly active pannus, plentiful sago-grain follicles, and papillary hypertrophy. In 3 cases, inclusion bodies could be demonstrated in epithelial scrapings. In all, the corneal ulceration cleared rapidly, pannus was reduced, and the follicles and papillary hypertrophy disappeared; but some inactive vascularized pannus remained. Three to 9 months after the end of treatment, subjective and objective improvement had been maintained in all cases. Five patients with chronic trachoma were given local aureomycin therapy; hyperemia was reduced and marked subjective relief afforded. Improvement continued even after the end of treatment.

Sakon<sup>76</sup> refers to unpublished work on trachoma by DeTucuman of Argentina and Kamel of Egypt, both of whom report dramatic results following the use of aureomycin.

Shah<sup>80</sup> has treated 75 patients with trachoma, using aureomycin borate drops. In all but 2 cases improvement was dramatic, and regression of pannus was observed in 6 cases. No effect on pannus was seen in the remaining 69.

Sarkies,<sup>77</sup> reporting from the Gold Coast, has compared a series of 31 cases treated with aureomycin with a series of 31 treated with

sulfadiazine, the remedy being applied in ointment form in both groups. He states that in every case not complicated by entropion, symptomatic relief was observed, but that it was rather more prompt and definite in the aureomycin-treated cases, and regression of the follicles was more striking. No effect on pannus was produced by treatment, but in some cases there was slight reduction in the caliber of the vessels, although not in the area of the corneal surface involved. Sarkies thinks that the greater efficacy of aureomycin may be due to its wider range of action against secondary invaders.

Desvignes and Morault<sup>33</sup> refer to the treatment of 40 patients by Pasca and Latte, using 0.5% drops or 1% ointment. Treatment was followed by very rapid disappearance of the conjunctival flora and of the inclusion bodies (in 24 hours), and distinct action on the pannus, but only slight modification of papillary hypertrophy.

The remarkable response of many cases of trachoma to aureomycin is well exemplified by a case reported by Beauvieux and his colleagues.<sup>10</sup> A young woman with generalized untreated trachoma came to the clinic hiding her eyes from the light with her hands, streaming tears, and complaining of feeling as if there were multiple foreign bodies in her eyes. Detailed examination was impossible except under local anesthesia. Aureomycin therapy was begun, with local instillations every 2 hours and oral administration of 3 Gm. a day. No other treatment was given. After 4 days, photophobia and lacrimation had completely disappeared, examination of the eye could very easily be made without anesthesia, and many of the follicles had disappeared, while others had almost completely flattened. The papillary reaction had practically vanished. After 16 days of treatment, all medication was stopped, and only a few papillae remained, with a few follicles in the corners of the upper lids. About 1 month later, the only evidence of previous infection that could be seen was a light pannus, with very fine new blood vessel formation. This combination of local and systemic aureomycin appeared to be particularly effective.

Bijl<sup>14</sup> states that it is untrue to say that aureomycin is ineffective in trachoma, simply because patients in the third or fourth stage of this disease are not cured. Treatment given in the early stage cures the infection, an extremely encouraging point for the future. He stresses the fact that infants are usually infected early in life by the mother and that treatment should be begun at this time, or at latest when the child is weaned. From a public health standpoint, it is extremely important that women be taught how to recognize the first stages of the disease in their infants, that they be made aware of the dangers of continued infection, and be familiar with the effective measures available for its treatment. Many children have already reached the third or fourth stage by the time they become adolescent. As an instance of what may be done to cure infection before the age of marriage, he mentions a school for infected children in Casablanca in which the hours of teaching are integrated with the hours of treatment, under competent medical supervision. Bijl feels that the control of trachoma in children is at present the pivotal point in the prophylaxis of trachoma.

Toulant<sup>83</sup> and co-workers have obtained less spectacular cures than those noted by some authors, but have found that aureomycin is of great service in acute serious forms of trachoma. They point out that at present utilization of aureomycin for large-scale therapy (particularly in sparsely populated, poverty-stricken areas) is limited by its price, by the instability of aqueous solutions, and by the necessity for frequent instillations; but state that it provides a local treatment which must not be neglected.

Van Tien<sup>86</sup> is of the opinion that a combination of mechanical brushing of the mucosa and topical aureomycin offers the best treatment at present available. This conjunctival scraping permits better penetration of aureomycin into the conjunctiva.

deAndrade<sup>30</sup> agrees that the classical methods of treating trachoma should to some extent be retained, and believes that local measures, such as mechanical destruction of granulations, diathermy coagulation, and irradiation, are of great value in limiting the late manifestations.

Naccache<sup>65</sup> lists the following advantages of aureomycin, which he believes make it the most suitable drug for the mass treatment of trachoma: economy; absence of toxicity; rapid effectiveness against secondary infection and complications; activity against the primary disease; simplicity of administration. He has obtained satisfactory results in 35 cases and feels that in trachoma I and early trachoma II, cure is possible by means of aureomycin ointment alone; for severe cases of trachoma II, he advocates local aureomycin and oral sulfonamide. He has found aureomycin very effective against complications such as pannus crassus and corneal ulceration.

### *Uveitis*

Alvis<sup>6</sup> found aureomycin valuable in the treatment of uveitis of obscure origin and of "viral" uveitis. Braley and Sanders<sup>21</sup> treated 18 patients with uveitis of various types, using local and oral aureomycin. Benefit was obtained in 8, the most striking examples being 2 cases of scrofuloderma combined with keratitis and uveitis. There was restoration of normal vision, and marked improvement in both the draining sinuses and the skin reaction associated with the underlying disease. In 2 similar cases still under observation, response of the cornea was prompt, but there was no change in the accompanying lymphadenopathy. One patient with recurrent uveitis and a positive Frei test, responded dramatically to aureomycin treatment. A recurrence took place 2 weeks later, but disappeared completely after a second course. Definite improvement was observed in 4 of 7 cases of uveitis of unknown origin; in 3 patients, there was no change.

Subconjunctival injection of aureomycin was used by Ainslie<sup>4</sup> in 2 cases of intraocular infection following operation. Both infections, one due to penicillin-resistant *Staph. aureus* and the other to *E. coli*, were controlled by aureomycin, but considerable permanent damage had already been done to the eyes.

Bellows and co-workers<sup>11</sup> observed recovery within 24 hours



in 1 case of acute iritis, and within 48 hours in another case, following the use of aureomycin and atropine. A third case of chronic relapsing uveitis, affecting both eyes, was treated during an acute exacerbation, without improvement.

Dollfus<sup>34</sup> has treated 9 cases of infection of the uveal tract with aureomycin, with very favorable results. The antibiotic, given orally, was graduated in dosage according to the age of the patient and the gravity of the infection. As a rule, the total dose was between 10 and 13 Gm. The response was good in 8 out of 10 infected eyes, rapid improvement beginning within the first 4 days of treatment. In a few cases, aureomycin was given for a few days as a collyrium as well as orally. Several of the patients had previously been treated unsatisfactorily by classical methods, and in the 2 cases in which aureomycin treatment failed, standard therapy gave no better results. One patient with secondary glaucoma resistant to pilocarpine responded in 48 hours to aureomycin and surface cyclodiathermy. Within 48 hours the intraocular tension had dropped from 60 to 25, and visual acuity passed from less than 1/10 to 10/10 in 8 days.

Von Sallman and co-workers<sup>87</sup> have reported good results in a case of granuloma of the iris, under treatment with cortisone and aureomycin.

Forbes<sup>38</sup> has given a remarkable example of the therapeutic action of aureomycin in a case of recurrent retinal detachment. Detachment of the retina occurred 3 months after successful surgical fixation, and systemic aureomycin, 250 mg. 5 times daily, given for 2 weeks brought about complete reattachment. Visual acuity was reduced, probably as a result of scarring from an old choroiditis.

Scheffler<sup>78</sup> has reported a case in which purulent endophthalmitis followed cataract extraction and required enucleation of the globe, since the other eye showed an early sympathetic ophthalmia. The infection in this eye was controlled by aureomycin, salicylates, local atropine and intravenous typhoid vaccine.

Culler and Clark<sup>26,28</sup> have made a clinical survey of the effectiveness of aureomycin in the prophylaxis of ophthalmia neonatorum, based on a consecutive series of 2,957 live births. In this series, 1.2 per cent of the children showed significant infection of the eyes during the first 7 days of life, as compared to 6.6 per cent observed by Thygeson in 1936, in a series of 3,939 newborn infants receiving Credé prophylaxis. In no case was infection serious enough to endanger vision, and it was due in only 1 case to *N. gonorrhoeae*. Most of the common causes of eye infection in the newborn were encountered. The 1 case of gonorrhea was treated satisfactorily with penicillin, 9 infants were treated successfully with aureomycin, and 2 infections cleared spontaneously in 24 hours. The authors recommend more extensive investigation of aureomycin prophylaxis by public health organizations, and suggest that the use of boric acid for washing the baby's eyes at home be replaced by instillation of 0.5% aureomycin.

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## INFECTIONS PRIMARILY INVOLVING MORE THAN ONE SYSTEM

**M**OST, if not all, of the infections discussed in this chapter, whatever may have been their portal of entry, spread rapidly through the blood stream to infect the entire organism. Localization in skeletal, visceral or soft tissue structures is therefore a logical part of these ailments, rather than the "complication" which it is usually considered.

Thalheimer<sup>304</sup> remarks that the choice of antibiotic is usually determined in large part by the organism present, but that there still remain many cases in which the germ cannot be isolated and in which it is unknown. He cites as an example the case of a young man with an intestinal infection of unknown origin. After many attempts to determine the cause and to treat the infection, he entered the author's service. Aureomycin was administered as the only antibiotic which had not yet been tried, and the response was spectacular. Thalheimer feels that when an infection fails to respond within a short time to a particular antibiotic, the medication should be changed, instead of attempting to overcome the infection with massive doses of the antibiotic which has failed.

Long<sup>187</sup> states that every year since its introduction, the dosage requirements for aureomycin have been decreased, and are now about 50% less than those suggested 2 years ago. This has not been the case with chloramphenicol.

## *Actinomycosis*

The actinomycetes which produce human disease are *A. bovis*, *Nocardia asteroides*, and a species of *Nocardia* which produces Madura foot. This group includes the only fungi which are susceptible to ordinary chemotherapeutic agents, a fact which is undoubtedly connected with the close relationship that this group bears to the bacteria. Aureomycin is active *in vitro*, *in vivo*, and clinically against these fungi.<sup>177,259,299</sup>

McVay<sup>205,207</sup> and co-workers have reported 3 cases of cervicofacial and 1 of abdominal actinomycosis with liver abscess, successfully treated with aureomycin without major surgical intervention. In 1 case of cervicofacial involvement,<sup>205</sup> not responsive to penicillin, aureomycin was given orally, 750 mg. every 4 hours, and at the same time applied locally in the form of a soft paste. The response was remarkable for its rapidity and completeness. In 48 hours the patient's temperature was normal and he was able to eat comfortably. By the twelfth day, the sinuses had ceased to drain and were beginning to epithelize. On the seventh day, local therapy was stopped. From the tenth to the twenty-eighth day, 500 mg. of aureomycin were given orally every 4 hours, and treatment was then discontinued. Six months later, there was no evidence of any lesion, except for a barely palpable induration at the site of a former sinus. One patient<sup>205</sup> had involvement of the mandible at the site of an extracted molar tooth. Neither the bone infection nor the facial mass had yielded to penicillin. After 3 months of illness, the patient was hospitalized; the fluctuant portion of the lesion was incised; and a small amount of pus was obtained, which yielded *Staph. aureus* on culture. Penicillin, a sulfonamide and hot saline soaks were used, but only slight improvement followed. A few days later, a positive culture for *Actinomyces bovis* was obtained. The patient was treated in the outdoor clinic with aureomycin for 28 days. Rapid improvement took place, and after 96 hours there was no further drainage. The patient was able to work

continuously during treatment; and 3 months after the end of treatment, he appeared to be cured.

Ten Berg,<sup>303</sup> noting definite improvement in 1 patient, believes aureomycin to be indicated in cases of actinomycosis resistant to ordinary therapy, and Wright and Lowen<sup>322</sup> have reported dramatic results with aureomycin in cervicofacial actinomycosis of 22 years' duration. In 6 days, the multiple draining sinuses had healed; in 14 days, there were no palpable lymph nodes; in 20 days, all masses had disappeared.

Ravina<sup>246</sup> observed very great improvement following the administration of a few grams of aureomycin, in a case of chronic actinomycosis with multiple fistula formation.

In a patient with actinomycotic abscess of the liver, observed by McVay and associates,<sup>207</sup> the symptoms had been of 2 years' duration, and even at the beginning a small abdominal mass had been observed. The patient had been comparatively well for some time after the first attack of gastrointestinal symptoms, but had an abrupt recurrence 2 months before being seen by the authors. Progressive increase in flatulence and constipation coincided with rapid growth of the abdominal mass. In the few weeks before admission, the patient had lost a great deal of weight and strength, and had some fever. Aspiration of a fluctuant area in the mid-line of the upper abdomen, corresponding to the left lobe of the liver, yielded thick yellowish-green material, containing sulfur-like granules and yielding *A. bovis* and *B. funduliformis*. The enlargement of the mass was such that the overlying skin was tight and shining, and it was thought that surgical drainage should be done at once. It was decided, however, to try repeated aspiration plus administration of aureomycin, intravenously and orally at first and later by mouth only. After each of the 3 aspirations that were done, aureomycin (500 mg. in 50 cc. of normal saline) was instilled. A week after beginning treatment, the material was found to be thin and odorless, negative for *Bacteroides*, but still positive for *A. bovis*. Four days later the actinomycetes had also disappeared. Except for

the development of cardiac decompensation a week after the start of treatment, readily controlled by digitalis and mercurial diuretics, the patient recovered gradually but steadily. No evidence of remaining infection could be found 11 weeks after the end of treatment, and the patient had gained over 40 pounds in weight.

Grant<sup>110</sup> has reported a case of actinomycosis of the jaw, in which symptoms dated from a fracture of the mandible, caused by a kick 3 months previously. Two weeks before admission, pain and swelling increased and dysphagia developed. Aspiration of a facial abscess revealed sulfur granules and *A. bovis*. As soon as the diagnosis was made, the previous treatment with penicillin and a sulfonamide was discontinued and aureomycin was begun. Improvement began within 5 days, and by the tenth day edema had subsided and the abscess had healed. Movement of the mandible was sufficient to permit the eating of solid food. After 1 month of treatment, the patient left the hospital against medical advice, only to return 3 weeks later for emergency treatment of a recurrence. Aureomycin was again given, and response was rapid. The abscess which had formed ceased to drain, and the patient was free of symptoms. At this time it was decided to remove a molar tooth which was in the fracture line. Convalescence was uneventful; but persistent, apparently nonactinomycotic, infection produced a small abscess and a sinus which was successfully excised. When last seen 10 months after his original injury, he was considered to be completely cured and the fracture was healed.

In a case reported by Kelly,<sup>167</sup> actinomycosis of the ascending colon was found 2 months after operation for a perforated appendix. Recurrent abscesses occurred in the right iliac and lumbar regions, and were followed by sinus formation. Penicillin and a sulfonamide in combination had no effect, nor did streptomycin. Ten months after the original operation, actinomycetes were found in the pus from an abscess. After 5 weeks of treatment with 3,000,000 units daily of penicillin, the patient appeared to be worse than before. Chloramphenicol brought about considerable im-



provement; but after a little over a month, relapse occurred and the organisms were again found in the pus. When aureomycin was substituted, marked clinical improvement was evident within a few days; the temperature remained almost continuously normal after the end of a week, and the patient rapidly gained weight. Aureomycin was continued for 3 months in all. Nine months after the end of treatment, the patient was apparently completely well and had been working for 4 months.

### *Boutonneuse Fever*

Boutonneuse fever, a tick-borne acute rickettsial disease, produced by *R. conori* and endemic in the Mediterranean basin, has been satisfactorily treated by means of aureomycin.<sup>16,128,172</sup> Although the untreated disease usually has a favorable outcome, aureomycin has been found to shorten the period of disability. Aureomycin may also be used prophylactically for the prevention of tick-borne rickettsioses in subjects exposed to tick bites, and should be continued for 3 weeks following exposure.<sup>308</sup>

The boutonuse fever of French Equatorial Africa is closely related to that of the Mediterranean and cross immunity exists between them. Le Gac and Rouby<sup>171</sup> have reported 2 cases of African boutonuse fever which yielded with astonishing rapidity and completeness to aureomycin, in the same way and in the same length of time as does Mediterranean boutonuse fever. In less than 24 hours, fever, headache and insomnia had yielded to aureomycin: within 48 hours, joint pains had disappeared and the rash was fading. In both these cases, infection was apparently transmitted by *Rhipicephalus sanguineus*, which infests all the dogs in that region.

### *Brucellosis*

Important steps toward the solution of the pressing public health problem presented throughout the world by brucellosis have been

made in the last few years. The economic loss from brucella infection in herds is a serious drain on a country's economy, and brucella infection in man is a source of much chronic ill health and invalidism. Until the use of aureomycin for this infection was begun, the best therapeutic attack was by a combination of streptomycin and sulfadiazine. Results with aureomycin have been superior. Its wide diffusion throughout the tissues enables aureomycin to reach brucellae in soft tissues, bones and joints, glands, and viscera; and its ability to penetrate the cell walls makes the brucellae within the cell susceptible to its action. The brucellae are obligate intracellular organisms, and can only be effectively attacked by an agent, such as aureomycin, which can pass the cell membrane.<sup>319</sup>

In the Silesia area of Poland, blood tests showed that 23.2 per cent of 146 veterinary surgeons reacted positively to brucella antigen. Of these, 32.4 per cent were asymptomatic; 32.4 per cent had the cutaneous form of the disease; and 35.2 per cent harbored a systemic infection. It appeared from the study that the most dangerous situation for contracting infection was during veterinary obstetrics. Kaminska and Szaffarski,<sup>150</sup> who report this study, recommend the periodical examination of veterinary surgeons to exclude brucellosis and, perhaps, the insuring of veterinary surgeons against brucellosis.

Aureomycin is effective in both the acute and chronic forms of the disease,<sup>4, 21, 24, 26, 35, 42, 43, 76, 116, 122, 133, 164, 170, 180, 236, 251, 257, 262, 286, 290, 311</sup> as well as against its complications,<sup>56, 107, 296</sup> and is considered the drug of choice.<sup>9, 296</sup> The more severely ill the patient, the better is his response.<sup>161</sup>

Rapid and constant improvement takes place on aureomycin therapy, both in the general and septicemic manifestations of brucellosis, and in skeletal and visceral complications, particularly those involving the liver and spleen. Janbon and Bertrand<sup>145</sup> note that in enlargements of glands and osteoarthritic complications there is increased resistance to treatment, and consider that, particu-

larly in the latter type of manifestation, vaccine therapy is advisable. They report that aureomycin administration was followed, as a rule, by permanent clinical cure in a series of 32 cases which they observed over a period of more than 6 months. The total relapse rate was 15 per cent. The relapses, occurring between 2 weeks and 5 months after cessation of the antibiotic, seemed to depend for their appearance upon the anatomical and clinical form of the original infection; i.e., on the presence of glandular or osteoarthritic foci, into which the antibiotic cannot penetrate.

Govantes Fuertes<sup>109</sup> observed disappearance of fever, of signs of systemic infection and of gross splenomegaly, in 1 case of brucellosis, within less than 48 hours after starting aureomycin treatment. The patient remained asymptomatic during 9 months of observation.

Spink and associates<sup>286</sup> found that in several cases a complicating polyneuritis, which made walking impossible, yielded rapidly to aureomycin treatment.

That aureomycin therapy marks a distinct advance in the treatment of brucellosis is indicated by the fact that over 90 per cent of the patients treated with this drug during a period of 2 years at the University of Minnesota Hospitals remained well after treatment.<sup>284</sup> Relapses still occur, but are less frequent and less severe than with earlier forms of treatment; a second course is generally adequate to produce permanent cure.

Amaniera<sup>4</sup> used aureomycin in 18 cases of brucellosis, including 3 chronic cases that were desperately ill; with results that were better than with any previous therapy, and with far fewer undesirable side effects than other effective remedies.

Signorelli<sup>277</sup> used oral aureomycin in a case of brucellosis which had lasted for 3 months and which had recently shown jaundice, ascites, and sustained high fever. Aureomycin acted rapidly to relieve the fever, the toxic state and the symptoms of hepatic insufficiency.

Perez Escudero<sup>231</sup> reports a case of brucellosis which had lasted

for 5 months without responding to intravenous vaccine, gold salts, neosalvarsan, streptomycin, autohemotherapy, or sulfonamides in high dosage. The patient had become gravely ill, with alarming symptoms of cardiovascular insufficiency. On the third day of aureomycin therapy, the temperature began to fall and soon reached normal; the circulatory disturbances improved, pain disappeared, appetite returned, and the patient felt so well that he did not wish to go on with treatment. A month later he suffered a fresh attack which was controlled by another course of aureomycin.

Conti and Cassano<sup>55</sup> have reported the results of aureomycin therapy in a number of cases of brucellosis with severe complications involving many systems of the body, and in some cases with severe hemorrhagic manifestations. Aureomycin administration resulted in rapid and complete relief of symptoms in all cases. Relapses were infrequent, very mild, and readily controlled by an additional course of treatment. They believe that these recoveries can be considered to be permanent, as in most cases they have lasted for a year.

Méndez Albarrán<sup>210</sup> describes a case of Malta fever with severe abdominal pain, putrid diarrhea, and an acute bronchitis which resembled virus pneumonia. The patient had not been able to sleep since the onset of his illness, but went to sleep shortly after the first dose of 250 mg. Ten hours after the first dose, all pulmonary symptoms had disappeared and the temperature was normal. Braude and Spink<sup>27</sup> believe that the protective action and the rapid clinical effects of aureomycin may be due to a primary antitoxic property.

The joint FAO/WHO\* Expert Panel on Brucellosis suggests a treatment schedule with aureomycin of 2 to 4 Gm. daily for 14 to 21 days, and similar treatment for relapses.<sup>309</sup>

An occasional obstinate case may benefit from the addition to aureomycin of streptomycin or sulfadiazine or both. Janbon and Bertrand<sup>145</sup> consider that results may be improved in brucellosis by

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\*Food and Agricultural Organization/World Health Organization

the association of aureomycin with streptomycin or a vaccine. Herrell and Barber<sup>132</sup> consider the most effective combination to be oral aureomycin and intramuscular dihydrostreptomycin.

Postiglione<sup>237</sup> has successfully used a combination of endovenous vaccine and oral aureomycin in 2 cases of brucellosis, and Balduini<sup>12</sup> considers that such a combination should bring about rapid and permanent disappearance of fever, by creating the most favorable conditions for definitive cure. He suggests that the addition of streptomycin to this therapy would permit a shorter period of treatment, with smaller dosage. Vaccine administration is well tolerated by the patient and in no way interferes with the activity of the antibiotics.

Greppi<sup>112</sup> proposes to administer combined treatment with aureomycin and specific vaccine to patients having visceral or osteoarticular localization of brucella infection, or having a tendency to relapse, or having been treated late with insufficient dosage of antibiotic. He recommends the administration of 1 or 2 Gm. of aureomycin daily for 6 to 8 days and, after a pause of 3 to 5 days, continuation of treatment with intravenous specific vaccine.

Sendas<sup>269</sup> has found a combination of aureomycin and sulfadiazine to be highly satisfactory. It often produces extraordinarily good results, through both the intensity of its effects and the rapidity with which they are obtained.

Sposito and Nava<sup>289</sup> have reported excellent results in 3 cases following intravenous administration of "microdoses" of aureomycin (50 to 250 mg. daily), and Stefanutti and co-workers,<sup>294</sup> using their technique, obtained similar results in 50 cases, some with serious complications.

Bondi<sup>22</sup> has reported a series of cases, to show that the treatment of brucellosis by very small doses of aureomycin given intravenously is free of danger, effective, and useful in clinical practice. He administers the drug, in a solution of 50 mg. in 30 cc. of 10% glucose at 12-hour intervals, twice daily. As soon as the patient has become afebrile, the administration is reduced to 1 injection daily.

Before each injection, he gives  $\frac{1}{2}$  mg. of adrenaline, to produce contraction of the spleen and put into circulation the greatest possible number of organisms, so as to render them available to antibiotic attack.

In a comparative study of various types of chemotherapy in 48 cases of brucellosis, Spink and co-workers<sup>286,287</sup> found that without question aureomycin was superior to the combination of streptomycin and sulfadiazine, and had the further advantage of causing no serious side effects. The over-all results with aureomycin were also an improvement over those obtained with chloramphenicol. The authors recommend that further investigations be made, using a combination of dihydrostreptomycin and aureomycin.

Pedro-Pons and Pedro-Botet<sup>229</sup> obtained prompt recovery in almost all of their cases of Malta fever. Relapse was quite frequent and they believe this frequency to be related to the rapidity with which the infection is suppressed, interfering with the development of an immune reaction. They feel that the association of streptomycin with aureomycin would be of considerable use in obtaining more solid cure and avoiding relapses.

Mazaré and Berthéas<sup>202</sup> surveying their own results and those of others in the treatment of Malta fever with aureomycin, have observed that final cure without relapse is more readily obtained in cases which are treated in the later stages of the disease. It is probable that these patients are able to develop a degree of immunity which aids in making cure complete.

Sicca,<sup>274</sup> who has studied the effect of antibiotics on the immune agglutinins in brucellosis, does not believe that relapses are caused by a failure to develop an immune response.

The temperature curve observed in the course of treatment of brucellosis by aureomycin is so characteristic that Desmonts<sup>80</sup> holds that the observation of such a curve would tend to confirm the diagnosis. During the first 2 days there is little modification; between the second and fourth day the temperature rises, the rise

being followed by rapid defervescence coincident with improvement in functional and systemic signs. This phase is followed by several days of apyrexia or hypothermia, after which the temperature remains normal, but with a rather greater than usual swing between maxima and minima. Desmonts considers that the febrile reaction in the early part of treatment marks a reaction to endo-proteins liberated by the massive lysis of the bacteria, and that the antibiotic action of aureomycin is in this way reinforced by a true endogenous vaccine therapy.

Vidcla<sup>312</sup> states that aureomycin controls the acute phase of brucellosis in 48 to 72 hours, and that relapses are mild and easily controlled. He recommends that treatment be given for 21 days, to a total of at least 42 Gm. He believes that careful supportive treatment and the addition of streptomycin or sulfadiazine to the medication enhance the good effects of aureomycin.

Molinelli and co-workers<sup>217</sup> have presented the results of their treatment of 46 cases of brucellosis treated with aureomycin. All but 2 of the cases were febrile, the other 2 evidenced pain in the lumbosacral area. Thirty-five of them had received no previous treatment, the remaining 11 had been given various standard forms of therapy, using 1 or more of the following: streptomycin, dihydrostreptomycin, a sulfonamide, PAB, transfusions, radio-therapy and intravenous vaccine. All 3 forms of brucellosis, *abortus*, *suis* and *melitensis*, were represented in this group. In all cases the temperature became normal between the second and seventh day of treatment, and the blood cultures became sterile, sometimes in the first 24 hours. Symptoms disappeared simultaneously with the disappearance of bacteremia. Notwithstanding this response, nearly 50 per cent of the patients relapsed, within periods ranging from a week to 6 months after treatment. All these relapses were mild and most patients became asymptomatic after a second course of aureomycin. In no case did the authors observe any new localization of the brucella infection in the skeletal or nervous system, and no infectious complications of any other type occurred. They feel

that treatment should be continued for at least 30 days, to a total of 70 Gm. or more, if the treatment is oral; 15 Gm. in 20 days or more, if treatment is intravenous; and 30 Gm., if the combined oral and intravenous route is used. They consider that the oral route is best for the average case, but that for very serious cases, or ones with painful complications, the intravenous route should be used. The immediate therapeutic results of aureomycin therapy they have found to surpass those obtained with any other treatment or combinations of treatment, with or without concomitant blood transfusions. The rectal route has been successfully used for the treatment of brucellosis in childhood,<sup>218</sup> although absorption is known to be variable.

Woodward<sup>319</sup> believes that since, with any therapy, brucellosis preserves its tendency to relapse, the aim of treatment should be to prevent this by 10 to 14 days of antibiotic administration during the acute attack, followed by 3-day courses at intervals of 3 months. Mouraret<sup>220</sup> suggests that aureomycin should be given in a dosage of 4 to 6 Gm. daily over a period of 15 days. Although the disease tends to have a long-drawn-out course, according to Debono<sup>71,72</sup> it is a self-limited infection, tending towards spontaneous improvement. In order to evaluate the success of any form of treatment, it is necessary to have a large number of cases with sufficient controls, and a long period of observation after treatment.

Some confusion may arise in the diagnosis of undulant fever. Brucellosis and infectious mononucleosis usually occur sporadically, and infectious hepatitis of viral origin may occur in non-epidemic form. All 3 diseases may be accompanied by obvious signs of hepatic dysfunction. Both brucellosis and mononucleosis are associated, in the active stage, with fever, lymphadenopathy, splenomegaly, and hepatomegaly. Since, during the initial stages of infectious mononucleosis, the leukocyte count may be normal or reduced, an added difficulty may be met in differentiating between this infection and brucellosis. The welfare of the patient demands that the doctor distinguish early between these 2 diseases,



since unrecognized and untreated brucellosis may cause chronic ill health, often with serious complications. Spink and Anderson<sup>285</sup> refer to a young man with congenital heart disease, who had been successfully operated upon a year previously for coarctation of the aorta, but who still had a cardiac murmur, fever and splenomegaly. Subacute bacterial endocarditis was diagnosed, but blood cultures were sterile at first and hematologic examination suggested infectious mononucleosis. The course of the disease, however, did not bear out this diagnosis and reinvestigation proved that the patient was suffering from acute brucellosis. Prompt treatment with aureomycin produced cure and the man was well 2 years later. The authors note that if the disease had not been recognized and treated, endocarditis might eventually have developed.

## *Cholera*

Aureomycin is effective against *Vibrio cholerae*.<sup>89</sup> Felsenfeld and associates<sup>90</sup> have found that effective cholera vaccines can be made, using organisms which have been killed with streptomycin, aureomycin or neomycin.

Seal and co-workers<sup>206</sup> have made a preliminary trial of intravenous aureomycin in the treatment of cholera. The test group consisted of 12 cases of cholera and 12 controls. All of the patients were in collapse when they were admitted 24 hours or less after onset, and little or no treatment had been given before admission. Because vomiting is so frequent in cholera, it was thought that a therapeutic amount of aureomycin might not be retained, if given orally, and the intravenous route was therefore used. At the beginning 100 mg. of aureomycin was given in each of 3 injections 6 hours apart. A slight rise of temperature was noted after the first dose, in most cases, and the dose was reduced to 50 mg. at each injection, with apparently even better results. Adjuvant treatment for dehydration and collapse was given in every case before beginning aureomycin and, in severe cases, was often supplemented by

coramine, atropine and alkaline saline solutions. The only difference in the treatment given to the controls was the omission of the antibiotic. For the patients given aureomycin, the average period of illness was reduced about one-third and the period during which vibrios were excreted was proportionately decreased. No significant difference in death rate was found in the 2 groups, but the patients receiving aureomycin were on the whole more seriously ill than those in the control group. In the treated group there were 11 severe cases and 1 moderate case, and in the control group, there were 4 severe cases and 8 moderate ones. The authors intend to make trial of the oral route in subsequent cases.

## *Diphtheria*

While diphtheria antitoxin counteracts the poisons of diphtheria, it has no effect on the bacteria, which may persist for a long time in the upper respiratory passages. Hence it is desirable to find an agent which will attack the organisms themselves. Streptomycin protects animals against diphtheritic infection; but it has toxic effects and permits the development of absolutely resistant strains of diphtheria bacilli.

The combination of antitoxin and penicillin has given good results in diphtheria. Satisfactory results (75 per cent+) have been obtained in the treatment of carriers by means of penicillin.<sup>153</sup>

Hewitt<sup>134</sup> demonstrated experimentally that aureomycin, whether given subcutaneously or orally, had some protective effect against *Corynebacterium diphtheriae*. Resistance did not develop in any strain tested. He suggested that aureomycin might be useful for the treatment of diphtheria carriers, since its oral administration would require a minimum of supervision.

Karelitz<sup>151</sup> states that in 5 acute cases of faucial diphtheria treated with aureomycin and antitoxin, nasopharyngeal cultures became negative, in 1 or 2 days in 3 cases, and in 4 days in 2 cases. One of these latter patients, an adult with very extensive mem-

brane formation, again had positive cultures 4 days after aureomycin was discontinued. Chronic corynebacterium peritonitis was reported by Rhoads<sup>248</sup> as having been cured by aureomycin.

Aureomycin and antitoxin were used by Karelitz and co-workers<sup>153</sup> in the treatment of 13 patients with faucial diphtheria, 25 to 50 mg. per kilo per day, plus antitoxin in severe cases, and nose and throat cultures were negative on an average of 5 days after treatment, as compared to an average of 21 days in previous cases treated with antitoxin alone. Aureomycin was effective in reducing the carrier period after diphtheria, and was successful in about 50 per cent of 11 diphtheria carriers. It did not, however, alter the toxic effects of the infection in 1 very sick patient, who developed a fatal myocarditis.

### *Infectious Mononucleosis*

Infectious mononucleosis is being diagnosed with increasing frequency and physicians are now recognizing that it is far from being as benign as it was formerly believed to be. Its course tends to be protracted and resistant to treatment, and is occasionally fatal.

Pelner and Waldman<sup>230</sup> observed an allergic background in every one of 50 cases of infectious mononucleosis studied by them, and suggest that the disease represents a special response by such persons to a virus infection, with the lymphatic system acting as the shock organ. They have used aureomycin successfully in 18 cases.

A large number of patients have been treated with aureomycin with good results: visceral and nervous system damage appears to be reduced to a minimum.<sup>13,44,113,147,193,267,268</sup> It is not to be expected that every case of infectious mononucleosis, without exception, will be cured by aureomycin, but it has been suggested that some cases not responding as desired have been treated with inadequate doses or at a late stage of their disease.<sup>154,245</sup>

Cronk<sup>64</sup> has studied the effect of aureomycin in cases of the

pharyngeal-glandular type. Thirty-two patients were treated and 30 left untreated as controls. All patients were observed in hospital for at least 24 hours before beginning treatment, in order to establish the diagnosis and the type of progress of the disease; symptoms often subside during the first 24 hours of hospitalization. After this interval aureomycin was begun, the only other drugs being analgesics. In many cases an abrupt drop in fever and symptomatic improvement coincided with aureomycin treatment. The antibiotic appeared to have little effect on objective findings and on the blood picture, and its use did not cut short the hospital stay. An interesting observation was that when pneumonia was present, improvement of both conditions followed promptly when aureomycin was given, and the response was much better than in uncomplicated mononucleosis.

Laureti and Agostini<sup>169</sup> reported a case of infectious mononucleosis very favorably influenced by aureomycin, and Capra<sup>99</sup> added 1 more case to the number of affirmative reports, stating that the rapid improvement which he observed was undoubtedly due to aureomycin and not to any spontaneous recovery.

Bijl<sup>19</sup> reported extremely rapid response of the temperature, general condition and blood picture in 1 patient treated with aureomycin.

Kimbrough<sup>159</sup> has treated 175 cases of mononucleosis with aureomycin and feels that symptomatic improvement has been produced regularly enough to warrant its use. The majority of cases of low-grade, chronic and subclinical infection, which are very difficult to treat, respond to aureomycin. One hundred twenty-four patients treated with aureomycin showed good response; a similar course was found only in 20 of 60 patients treated symptomatically. Twenty-two of the latter had a lengthy, severe illness as compared to only 14 of the aureomycin-treated subjects.

Delgado Correa and Volpe,<sup>75</sup> surprised by the excellence of the results obtained with aureomycin in infectious mononucleosis, and its lack of toxicity, recommend its use in all cases of this

infection. In 1 seven-year-old child, ill for 3 weeks, fever disappeared 17 hours after beginning treatment, and the blood picture became normal in 8 days.

Carter and Sydenstricker<sup>41</sup> have reported their experience with aureomycin in 9 cases of infectious mononucleosis. Eight of the patients had pharyngeal involvement and improved strikingly after aureomycin had been begun. It was necessary to give aureomycin intravenously to 1 patient until he was able to swallow, and the severe angina responded impressively. All of the patients felt well within 24 to 72 hours. The benefit produced by aureomycin seemed to be independent of the stage of the illness at which it was started. The authors consider that 1 Gm. of aureomycin initially, followed by 0.25 to 0.5 Gm. every 4 to 6 hours, for 5 or 6 days, should provide an adequate course of treatment.

Vaisberg<sup>310</sup> considers aureomycin to be the most valuable agent available for the treatment of infectious mononucleosis, and suggests that adrenal cortical extract may be valuable for the extreme asthenia associated with this infection. He used both of these remedies in 1 case of severe mononucleosis, which had become worse during treatment with chloramphenicol and adrenal cortex. When chloramphenicol was stopped and aureomycin begun, marked improvement followed within 48 hours. Vitamin B<sub>12</sub> was also given by injection because of severe inflammation of the tongue. The patient had a smooth convalescence and was well in 2 weeks.

Malhotra<sup>195</sup> has described 4 cases of acute infectious lymphocytosis in adults, presenting as an acute lumbago, with radiculitis and changes in the cerebrospinal fluid. This disease is now believed not to be identical with infectious mononucleosis. In 3 cases given aureomycin, the symptoms and the lymphocytosis were quickly controlled, within 5 days at the outside; while in 1 patient not given aureomycin, the pain continued for 4 weeks, and the lymphocytosis for 5 weeks, from the onset. The patient was not able to get out of bed until the end of the fourth week.

In order to arrive at a fair estimate of the effects of aureomycin in this condition, a large series of well-controlled cases should be studied.

## *Leprosy*

Leprosy is a systemic disease, manifesting itself chiefly as dermatological lesions, neurologic damage and ocular changes. The percentage of ocular involvement is higher than in any other systemic disease. It appears early in the course of the infection and is considered by many investigators to be pathognomonic.<sup>86</sup> The low incidence of ophthalmic disease reported by previous writers depends on the fact that the slit lamp is required to diagnose early changes. Elliott<sup>86</sup> believes that with adequate examination more than 90 per cent of sufferers from leprosy will show ocular changes. He strongly disagrees with the current concept of the low infectiousness of leprosy and points out that the incubation period can be less than 4 years, and may even be less than 2. Elliott stresses the importance of awareness of the contagiousness of this disease, for its eradication, and of concentrating on the early diagnosis and treatment of cases occurring among veterans of the Korea fighting, in order to prevent the establishment of infection in this country. He thinks it possible that in South Korea there are as many as 35,000 cases of leprosy in its advanced contagious form.

The principal eye changes in leprosy are: nodules along the course of the filaments of the corneal nerve, limbal leproma, keratitis, iritis, cataract, and nodules on the fundus of the eye. The acute episodes of "iritis" seen in leprosy have many points in common with glaucoma. Pilocarpine is more effective than atropine, and subsidence of the process is hastened by supportive therapy with an antibiotic such as aureomycin and increased dosage of sulfones.

The curative action of aureomycin on the ocular manifestations of leprosy suggested the desirability of study of its effect in

the systemic disease. Palomino and co-workers<sup>227</sup> were unable to observe any significant changes in 2 cases of lepromatous leprosy treated intensively with aurcomycin for 6 and 7 weeks. However, the time required for the elimination of bacilli from the lesions of leprosy is exceedingly long with any known type of effective therapy, being measurable in months or years, rather than in days or weeks.

Johansen and Erickson<sup>146</sup> state that 5 patients, treated with 1.0 to 1.5 Gm. of aureomycin daily for 1 year, progressively improved. All showed healing of surface and mucosal lesions and all gained weight.

More data are obviously required before an opinion can be expressed on the usefulness of aurcomycin in leprosy.

## *Leptospirosis*

The leptospirae are apparently worldwide in distribution, and comprise a large number of species, many of which have been known to cause disease in man. Most of the cases so far recognized in America and in Britain have been due to *L. icterohaemorrhagiae* (Weil's disease) and *L. canicola*. Since meningitis is one of the outstanding symptoms of human leptospirosis, Broom<sup>31</sup> examined sera from 642 cases of "aseptic" meningitis, sera which had already been tested to exclude virus infection. Nineteen cases showed infection with leptospirae, 17 of them being Weil's disease and 8 canicola fever. Since the middle of 1947, there have been 465 cases of Weil's disease diagnosed in the United Kingdom, and 70 cases of canicola fever.

The leptospirae, although primarily parasites of rodents, may become adapted to domestic animals, in whose kidneys large colonies may exist without harm to the host. Human cases are therefore likely to occur in workers in rat-infested areas, in agricultural laborers, in food handlers and in persons bathing in contaminated water. Antiserum is a valuable form of treatment, if

given in the first few days of illness, and penicillin has been beneficial in a number of human cases.

Aureomycin, in an oral dose of approximately 50 mg. per kilo every 12 hours, is fully effective in the treatment of chronic carriers of canine leptospirosis in hamsters and dogs.<sup>211</sup>

Siebert<sup>275</sup> found that although *Leptospira canicola* was much more resistant than *Leptospira icterohaemorrhagiae* to aureomycin *in vitro*, animals experimentally infected with either of these diseases were protected by 0.5 mg. of aureomycin per 50 Gm. of body weight. Death in 7 days was produced by the same cultures when antibiotic protection was not given. Serous meningitis, which is frequent in leptospirosis and which is thought to be caused not by the organism but by an antigen-antibody reaction, did not appear to be influenced by aureomycin, but Siebert found that all other signs and symptoms disappeared with great rapidity as soon as aureomycin was begun.

In a comparative study of the value of various antibiotics in the treatment of 67 cases of leptospirosis in Puerto Rico, Hall and co-workers<sup>118</sup> were unable to demonstrate a curative effect for any of the broad-spectrum antibiotics. They used chloramphenicol, penicillin, streptomycin, terramycin, and aureomycin, alone or in combination with streptomycin or cortisone.

*Weil's Disease*—Prompt and satisfactory recovery from Weil's disease on aureomycin therapy has been reported by a number of authors.<sup>14, 25, 115, 160, 192</sup>

Broom<sup>31</sup> has used aureomycin in 3 cases of Weil's disease, with 2 recoveries and 1 death.

Sposito and Nava<sup>289</sup> consider that aureomycin has a specific action upon leptospirosis. They recorded cure in 1 extremely severe case with azotemia and hepatorenal syndrome.

Batchelor and Todd<sup>14</sup> gave aureomycin to a patient who had become steadily worse in spite of massive penicillin therapy and who appeared moribund. Three days later, he was convalescent.



Similar results were obtained by Lurie<sup>192</sup> in another critically ill patient.

Mills<sup>215</sup> reported the isolation of *Leptospira icterohaemorrhagiae* from the urine of a sewer worker with marked hyperpyrexia and jaundice, and with signs of meningeal irritation. He showed marked episcleral injection, a feature which seems to be common in Weil's disease, often with subconjunctival hemorrhage. The patient had a somewhat lengthy illness but made an uninterrupted recovery under treatment, first with penicillin and then with aureomycin.

*Canicola Fever*—In canicola fever treatment was mainly symptomatic until 1946, and of the remedies introduced since that time, only aureomycin has been reported as effective. Stagg and Leibovitz<sup>291</sup> treated 1 case with aureomycin, and noted dramatic relief of symptoms within 24 hours and complete remission of all symptoms in a week. Observation for 3 months after discharge showed no evidence of relapse or of a carrier state.

Whitehouse<sup>315</sup> has also written of the clinical effectiveness of aureomycin in the treatment of canicola fever. He gave aureomycin to a severely ill man who was disoriented and incontinent of urine, and who was thought on admission to be suffering from infectious hepatitis and pneumonitis. Weil's disease was suspected on account of the icterus which was present, but no history of contact with rats or dogs could be elicited. However, the neighborhood of his home was known to be infested with rats. On the third day in hospital, while the jaundice seemed to be fading, severe hemorrhagic conjunctivitis developed. Penicillin had been started on admission but, because of the continued spiking temperature and of the possible presence of Weil's disease, aureomycin was given on the third hospital day. The patient's temperature dropped gradually and he was afebrile in 48 hours. The organism could not be identified, but serologic tests indicated infection with *L. canicola*. The patient improved steadily but, when aureomycin was stopped,

fever returned. A second course of aureomycin produced apparently complete recovery, both clinically and according to laboratory tests, although the patient continued to run some fever during convalescence. The author believes that aureomycin is at present the drug of choice in leptospiral infections and suggests that it be used in all patients suspected of such infection.

### *Listeriosis*

Listeriosis is predominantly a disease of lower animals, but cases have been reported in man. Aureomycin is effective in inhibiting the growth *in vitro* of *Listeria monocytogenes* and of protecting mice infected with this organism.<sup>111</sup> It appears to be more efficacious than chloramphenicol.<sup>226</sup> Zink and co-workers<sup>327</sup> found that *in vitro* the organism is very sensitive to aureomycin, and resistant to terramycin, penicillin, chloramphenicol and streptomycin. A dose of 5 mg. per kilo of body weight for 4 days gave absolutely complete protection against experimental infection in mice. No protection whatever was afforded by penicillin in doses of 10 mg. per kilogram of body weight. Although no report on the use of aureomycin alone in human cases of listeriosis has as yet appeared, this note on the disease is included here as a therapeutic suggestion to any reader who may encounter a case in man. One case of *Listeria meningitis* in an infant has been cured by combined treatment with aureomycin and penicillin.<sup>183</sup>

### *Malaria*

There is no doubt that aureomycin possesses definite antimalarial activity, although it is as yet too early to judge of its lasting effect. A number of cases have been treated with satisfactory results, the chief action appearing to be on the exoerythrocytic states.<sup>225</sup>

Experimental malaria (*Plasmodium berghei*) in rats produced

death of controls in about 7 days. Rats given 3 doses daily of 15 mg. of aureomycin survived for an average of 24 days. When 12 daily doses of 15 mg. each were given orally, there was no appearance of the parasite in the peripheral circulation during an observation period of 60 days. It was absent from the viscera of rats sacrificed on the fifteenth day. Aureomycin has a similar activity against *P. gallinaceum*<sup>52</sup> and *P. vivax*.<sup>58, 141</sup> Aureomycin is active against the erythrocytic forms and the exoerythrocytic forms, early or late, of *P. gallinaceum* in the chick.<sup>52</sup> It therefore has both a therapeutic and a prophylactic effect. Complete eradication of the infection was not obtained, but aureomycin was able to prevent death from exoerythrocytic forms, an effect previously obtained only with pamaquine, pentaquine, paludrine and sulfadiazine.

Partial protection of human volunteers against vivax malaria was obtained by Cooper and associates<sup>58</sup> with a daily dose of 8 Gm. of aureomycin. The men did not develop malaria until 30 and 31 days after exposure, while 4 controls bitten by the same mosquitoes developed infection in 12 to 14 days. The controls were treated with aureomycin after patent infection had appeared, but action of the antibiotic was too slow to be of practical value. The authors concluded that aureomycin does not eradicate the fixed-tissue stage of *P. vivax*.

Nor El-Din<sup>225</sup> found that when aureomycin was given to 6 patients with benign tertian malaria and 1 with malignant malaria, asexual forms in the blood gradually decreased in number, and disappeared in 2 to 5 days. Gametocytes usually persisted for a couple of days longer. Fever disappeared on about the third day of treatment. Subsequent bouts of fever either did not occur or were very mild. Except in the case of malignant malaria, the spleen shrank rapidly to almost normal size. The patients were still under observation at the date of writing, to determine the incidence of relapse.

## *Measles*

Dowling and co-workers<sup>82</sup> treated 9 cases of measles with aureomycin, and obtained encouraging results. In 3 cases treated while Koplik's spots were present, 2 of the patients were afebrile and asymptomatic within 24 hours, and the third within 36 hours. The rash appeared as usual, but disappeared rapidly. In 6 patients treated after development of the rash, there was a rapid fall of temperature, and subsidence of symptoms in 24 hours.

Drake and his associates<sup>84</sup> reported remarkable benefit from the use of aureomycin in 12 cases of measles. The drug was given orally to 11 patients in 0.25 Gm. doses, every 4 hours at first and then every 6 hours. The twelfth patient was so acutely ill that aureomycin was given intravenously for the first 2 doses. In all cases, photophobia was abolished within 24 hours, and rectal temperatures were normal in 28 hours or less. Six controls had photophobia for 48 to 96 hours, and fever for 72 to 120 hours.

Knight<sup>162</sup> was unable to detect any significant beneficial effect with aureomycin in 10 cases of measles.

Encouraged by the results of Dowling and Drake in rubella, Karelitz and co-workers<sup>152</sup> studied the effect of aureomycin in a larger series of cases. Aureomycin was given to 45 children ranging in age from infancy to 9 years; penicillin was given to 44, both for evaluating its effect on early measles and as a control for the aureomycin group; and 43 children were left untreated. Both aureomycin and penicillin tended to reduce the temperature, the duration of fever being 2.2, 2.8 and 4.4 days respectively in the aureomycin, penicillin and control groups. Aureomycin produced a more rapid drop in temperature than did penicillin, although it seemed to be without effect on the duration, pattern and intensity of the rash. Neither rhinitis, photophobia nor cough was appreciably affected by antibiotic treatment. However, in the patients treated with antibiotics, convalescence was usually uneventful; while in untreated cases there were many complications. Compli-

cations were present at the beginning of treatment in some cases, in both treated and untreated groups. In 23 per cent of the untreated patients, complications developed during the observation period. Complications in general responded to aureomycin treatment. Two cases of croup recovered after 6 days on aureomycin. No complications developed during aureomycin therapy, but 1 patient developed otitis media during penicillin therapy. The authors believe that aureomycin and penicillin are chiefly of value in the prevention and cure of secondary infection in rubeola.

El-Din<sup>85</sup> made a comparative study of measles therapy in an epidemic occurring 1 year ago. He found that while aureomycin does not prevent the appearance of the rash, it may reduce its intensity if given early. When aureomycin was given before the rash developed, the fever rapidly dropped, and the catarrhal stage lasted only about half as long as usual. El-Din found aureomycin, penicillin and sulfadiazine to be about equally effective in preventing complications.

### *Melioidosis*

Melioidosis is a glanders-like disease which only occasionally appears in man. Clinically, it may take either the acute or subacute septicemic form, which is seen in the vast majority of cases and is usually fatal, or the chronic form, which is rare and whose course generally follows that of the more common mycotic infections. Garry and Koch<sup>90</sup> have used aureomycin orally and tyrothricin locally in a case of chronic melioidosis, involving the skin and resembling in many ways a *Ps. aeruginosa* infection. The treatment seemed to produce favorable response, with improvement in the general condition and healing of the skin lesions.

### *Mumps*

In contrast to mumps in childhood, which except for the possible development of encephalitis, is an illness requiring no special super-

vision, mumps in the adult is often serious, orchitis being a common complication, with marked deterioration in the general condition. Bilateral orchitis, though infrequent, is important on account of the sterility which may result. Schmuttermeyer and co-workers<sup>261</sup> report the case of a twenty-nine-year-old physician, with severe inflammation of both testes. Previous treatment with penicillin and the sulfonamides had not prevented the development of inflammation in 1 testis on the seventh day of the disease, inflammation of the other having occurred on the third day, before treatment was started. Three hours after beginning aureomycin, there was an abrupt return to normal temperature, associated with rapid general improvement and decrease in testicular swelling. The orchitis which appeared later never reached the same degree of swelling as did the one which had begun on the third day. After 5 days of treatment, the patient was practically well, and was able to leave his bed.

Schaub<sup>260</sup> compared the course of 11 uncomplicated and 6 complicated cases of mumps treated with aureomycin, with that of 17 untreated patients. He concluded that the early administration of aureomycin to adult patients with epidemic parotitis prevented the development of complications and favorably influenced the course of the disease. Complications already present, such as orchitis and pancreatitis, were rapidly relieved. No case of meningitis was seen in this series of patients.

Woodward and associates<sup>320</sup> observed remarkable improvement in 24 hours, in 3 adult cases of mumps treated with aureomycin. Spinelli, Cressy and Kunkel<sup>63,283</sup> reported great benefit in 4 cases, all with orchitis and 2 severely toxic. Fever, symptoms and testicular tenderness had disappeared in all cases within 36 hours. These authors note that the rapid disappearance of edema and swelling of the testis, resulting from the use of aureomycin, makes it reasonable to assume that the use of this antibiotic may prevent the development of sterility as a sequel to mumps orchitis.

In adult mumps, the combination of parotitis, meningoenceph-

alitis and orchitis is comparatively rare. Pitman and associates<sup>235</sup> have reported 1 case. Aureomycin seemed to have no effect on the course of the disease; but, it should be noted that bilateral parotid swelling had appeared 8 days before admission, so that treatment was instituted at a comparatively late stage.

Shane and Sodero<sup>270</sup> were unable to observe any benefit from aureomycin in a case of mumps in a four-year-old boy. Two patients reported by Mazursky and co-workers,<sup>203</sup> with known exposure to epidemic parotitis, developed the disease early in the incubation period, while being given aureomycin for another infection.

Deming<sup>78</sup> advocates the use of aureomycin and of female sex hormone, given daily for 5 days as soon as mumps is diagnosed in the adult male. The early use of this hormone, he believes, will halve the complications of orchitis, but if orchitis is already present, it is of little or no value.

## *Newcastle Disease*

The virus of Newcastle disease of fowl can produce infection in man. The infection usually takes the form of a conjunctivitis, although it may appear as an atypical pneumonia. Very rarely there may be neurologic involvement. Most human cases recover in 5 to 14 days.

It must be emphasized that the conjunctivitis of Newcastle disease is only part of a systemic infection. Local treatment with aureomycin and penicillin, in cases where the infection has first manifested itself in the eye, appears to be of no use, according to Gettes<sup>102</sup> and to Keeney and Hunter.<sup>156</sup> Lépine and co-workers<sup>176</sup> state that, although this appears to be partially true, the course of the disease is longer in an untreated eye than in an eye treated with aureomycin.

The last group<sup>176</sup> has reported 3 cases of accidental laboratory infection with this virus; in all 3, the infection appeared within 20

to 30 hours. It began abruptly, and took the form of a very severe conjunctivitis, ushered in by severe ocular pain. Two of the patients were treated on the second day by means of local instillations of aureomycin drops, the third was given a standard form of treatment. The course followed by all 3 patients was very similar, so that superficially it would seem that aureomycin had produced little effect. However, the 2 patients treated with aureomycin had received massive bilateral contamination, while in the third patient the contamination was lighter and unilateral. Furthermore, all attempts at isolating the virus failed after treatment with aureomycin had been begun, and egg inoculation produced no growth, while in the third patient, the virus could be isolated directly from the conjunctival exudate on the second and third days. The authors conclude that conjunctival instillation of aureomycin prevents generalization of the infection, confining it to local manifestations; and that it also hinders the development of immunity, since the only patient showing neutralizing antibodies in the serum was the one who was not given aureomycin.

### *Pancreatic Fibrosis* (Mucoviscidosis)

Pulmonary complications are frequent and serious accompaniments of fibrosis of the pancreas. The X-ray characteristically shows atelectasis and emphysema. In the later stages of the disease, bronchiectasis and multiple staphylococcal abscesses may develop. This disease has a familial tendency and its etiology is unknown. Accordingly the treatment is supportive and symptomatic. For the inevitable respiratory infection, aureomycin is of the greatest value.<sup>137</sup>

It is possible that the pulmonary involvement in pancreatic fibrosis begins shortly after birth. It reaches its highest intensity between 6 and 18 months of age, and then tends to subside, so that children surviving from 5 to 8 years may become free of pulmonary complaints, although not, of course, cured of the pancreatic dysfunction.<sup>201</sup>



According to Déchêne,<sup>74</sup> the outlook for children suffering from pancreatic fibrosis is strikingly improved by a regime of protein milk, partially-skimmed evaporated milk, cheese, meat, pancreatin, vitamin A, aureomycin and prostigmine.

Gibbs<sup>103</sup> has mentioned the case of a five-year-old girl with fibrosis of the pancreas, in whom cardiac failure with electrocardiographic evidence of cor pulmonale developed. She improved under therapy with digitalis, pancreatin, antibiotics, and sulfamerazine. Penicillin was at first effective, but later its activity diminished. The patient then responded well to aureomycin.

Shwachman and co-workers<sup>271</sup> have reported the successful use of aureomycin in 35 cases of mucoviscidosis, all having *Staph. aureus* in the nasopharynx. Many of these children, whose ages ranged from 5 weeks to 12 years, had been treated by dietary methods for years. The response in 24 cases was excellent; in 5, good; in 2, fair; and in 4, absent. In 31 of the 35 cases, there was noted, within 2 or 3 days of the first dose of aureomycin, definite relief of cough and dyspnea, reduction of fever, and marked increase in weight, appetite, and sense of well-being, even though diarrhea persisted in some cases. The authors emphasize that regular and continuous administration of any antibiotic is required to prevent relapse, so that aureomycin, which can be given for long periods orally with little fear of development of hypersensitivity or of the appearance of drug-fast strains, appears to offer the ideal therapy for this disease. The inhibitory action of this antibiotic on the intestinal flora may interfere with the synthesis of necessary vitamins and, for this reason, long-term aureomycin treatment should be accompanied by the use of vitamin supplements.

An evaluation of the maintenance treatment of fibrocystic disease of the pancreas with aureomycin has recently been made by Stowens.<sup>297</sup> Seventeen children, 2 months to 7 years of age, were given aureomycin as the sole remedial agent over periods of 12 to 24 months. The diet was not restricted except for the elimination of gross fats; and it was supplemented with about 3 times the

recommended daily intake of fat-soluble vitamins and a high proportion of water-soluble vitamins. At the beginning, the children were small and malnourished, and signs of progressive respiratory disease were present in all but 3, 2 of them infants. Two children with advanced bronchiectasis died during the course of study, 1 of pertussis at the age of 19 months and the other at 6 years of age, of myocardial failure secondary to probable cor pulmonale. The children, on the whole, remained remarkably free from respiratory infections, and no worsening of pre-existing respiratory disease has been evident. All of the 8 children with minimal respiratory difficulties at the beginning improved clinically; and of 4 patients who had advanced pulmonary disease, all have improved subjectively and objectively. Two of the children, who were previously kept in bed most of the time, now attend school regularly. In all cases, gain in height and weight was very satisfactory, and appetite was almost ravenous. No changes were noted in pancreatic function or in the character of the stool. Striking improvement in personality and behavior were reported by the parents and observed by the physicians. The uninterrupted administration of aureomycin over long periods of time produced no undesirable side effects. To maintain the patients in the desired state of health, it was necessary to keep the dosage at levels of 25 mg. per kilo daily, given in 2, 3 or 4 doses. Two studies of nitrogen balance were performed on each of 4 patients. When aureomycin was administered, the amount of nitrogen retained increased 14-fold, as a result of an increase in the amount of protein eaten, in the amount of nitrogen absorbed, and in the utilization of nitrogen. The mechanism by which aureomycin produces this tremendously increased utilization of protein is obscure. Similar effects on nitrogen balance and on growth have not been reported following the use of other antibiotics, according to Stowens.

In a study of 30 cases receiving 250 mg. of aureomycin daily, Bruyn<sup>23</sup> noted improvement in appetite and weight-gain in most cases, and decrease or disappearance of cough in 18 children. Nine

other patients did better on aureomycin than on any previous form of treatment. Ten children who were started on aureomycin within 6 months of the onset of clinical disease followed essentially the normal course for their age, in growth and well-being.

Recent experience, therefore, offers hope for the survival of more children beyond the often fatal first 2 years.

## *Plague*

Aureomycin provides greater protection, experimentally, against the toxins of *Pasteurella pestis* than do penicillin, streptomycin, chloramphenicol or sulfonamides.<sup>239</sup>

In experimental animals with *P. pestis* septicemia, aureomycin saved 9 out of 10, all controls dying within 8 days. Oral aureomycin was found to be 8 times as effective as oral chloramphenicol, mg. for mg., and was as effective as streptomycin given subcutaneously. The oral dose of aureomycin required for cure was 4 times as great as the curative subcutaneous dose of streptomycin.<sup>282</sup> One human case of plague in Arizona recovered on combined penicillin and aureomycin therapy.<sup>167</sup> Ramachandran<sup>241</sup> gave aureomycin to 15 plague patients in a hyperendemic region of Hyderabad, and obtained cure in 12. Bubonic plague was present in 12 cases, and septicemic plague in 3. Death occurred in 6 hours or less after admission in 2 patients with septicemic plague, and in 1 with bubonic plague, who was comatose and died in 1 hour, following hemoptysis. In all the other patients, many of them comatose on admission, the response to oral aureomycin was good, temperatures becoming normal in 3 to 8 days.

Rosenstiel and Bateman<sup>254</sup> have reported cure with aureomycin, dihydostreptomycin, sulfadiazine and sulfamerazine, in a case of bubonic, septicemic and pneumonic plague. Such cases usually end fatally in 3 or 4 days. The patient was given aureomycin on the fifth day of his illness. Within 24 hours he reported subjective improvement, but since there was no appreciable objective change,

the additional therapy was instituted on the sixth day. On this day, the patient began to take some nourishment. Six days after admission (eleventh day of illness) the patient was very greatly improved, and from that time convalescence was rapid. Antibiotic treatment was continued for a total period of about 3 weeks, 62 Gm. of aureomycin and 25 Gm. of dihydrostreptomycin having been given.

Plague has been reported from 15 of the western United States and human cases appear to be increasing in number. Link<sup>184</sup> observes that 5 cases occurred in the year 1950. Recovery took place in 3 patients, 2 of whom were given aureomycin in addition to streptomycin and sulfadiazine. Penicillin appeared to be inadequate for treatment, since the 2 fatal cases had been given penicillin only. Further clinical work is needed.

### *Poliomyelitis*

Most physicians engaged in treating poliomyelitis have been unable to see any significant benefit when aureomycin is given. However, Crowley and Jackson<sup>67</sup> feel that they have demonstrated a direct effect on the course of patients with poliomyelitis, from the use of a combination of intravenous aureomycin and Amigen, given alternately. In severe cases, both solutions are given continuously and slowly in opposite arms at the same time. In a series of approximately 100 cases seen during 1949 and 1950, 23 patients were treated in the above manner. No contraindications for the treatment appear to exist. The authors give details of 13 cases, 5 of them routine types and the remainder severe paralytic cases, most of them having bulbar involvement. In every case the progress and spread of the disease was halted in 48 hours.

In 1949, they<sup>66</sup> gave aureomycin intravenously to 10 patients with poliomyelitis, on account of its usefulness in the treatment of some virus diseases. The indications for its employment were: signs of bulbar or cervical involvement, persistent vomiting, evi-

dence of increasing severity of the disease. Amigen was administered intravenously, to maintain protein balance, to prevent cerebrospinal edema, and perhaps to prevent toxic effects of protein breakdown in the central nervous system. Amigen and aureomycin were given to 6 patients with bulbar or cervical paralysis and to 1 with cerebral and vesical involvement, who immediately began to improve; and to 3 patients with lower limb paralysis, stopping progression of the disease within 48 hours. Aureomycin alone administered orally to 12 cases had no appreciable effect on the course of the illness. Before the establishment of the combined therapy, 4 cases of bulbar poliomyelitis had been reported in the community in that year and all were fatal. Therapy with aureomycin and Amigen stopped the progression of the disease within 24 hours, produced definite improvement within 72 hours, and had caused such notable regression of symptoms in 6 days, that medication was stopped. No patient had to be put in a respirator.

## *Q Fever*

Q fever, recognized first in Australia in 1937, is now known to be of worldwide occurrence and of considerable practical importance. It is an acute febrile disease, generally with mild respiratory symptoms. Pneumonia may be demonstrable by X-ray in hypersensitive cases. While usually a benign infection, severe cases with complications do occur and may be fatal.<sup>125</sup> The infection is very resistant to penicillin and to the sulfonamides, but has been effectively treated with aureomycin without the appearance of any complications.<sup>25,34,37,79,125,173,175,240</sup> If relapse follows, it can be controlled by resumption of aureomycin treatment.<sup>281</sup> The chronic form, which is apparently rare but which is known to occur (and may occur more often than it is suspected), is also curable by aureomycin.<sup>46,94</sup> Many physicians consider aureomycin to be superior to any previous form of therapy used for this disease.<sup>23,125,276</sup>

Aureomycin is particularly valuable when employed early,<sup>276</sup>

before there has been time for definite serologic diagnosis, so that it must often be given on mere suspicion of Q fever. However, since it produces little or no interference with antibody formation, a positive diagnosis can be made serologically, even after recovery.<sup>28</sup>

Feldman and co-workers<sup>68</sup> discussed a small epidemic of Q fever, occurring in a rendering plant in Syracuse, New York. Five of the patients were given aureomycin from the first and responded rapidly, while in 5 others who failed to respond to other remedies, the disease appeared to be terminated abruptly by aureomycin.

Clark, Lennette and Meiklejohn<sup>49</sup> have summarized the results of aureomycin treatment in 45 patients treated by them during the year 1950. They have compared the results with the data on 25 patients with proven Q fever seen in 1948 and 1949, who were treated with penicillin and whom they therefore consider as equivalent to untreated patients, since penicillin appears to exert no significant influence on this infection. The patients receiving aureomycin could be divided into 3 groups, according to their response to treatment. Seventy-one per cent of the patients became afebrile in 5 days or less, as against 28 per cent of those treated with penicillin; 9 patients did not become completely afebrile in 5 days but showed a decided decrease in fever and subjective improvement (this type of effect was not observed in the penicillin group); 4 patients showed either very slight improvement or none at all. It is thus evident that aureomycin has a definite place in the treatment of Q fever, although it is not invariably effective. It is thought that there may be several strains of *C. burnetii* with differing sensitivities to aureomycin. The oral dosage of aureomycin used in this series was 2 to 4 Gm. per day and the intravenous dosage either 200 or 300 mg. per day, given in 2 doses. The authors suggest that possibly increased amounts of aureomycin may be indicated in the treatment of Q fever.

Forbes<sup>93</sup> observed rapid response to aureomycin in 1 severe case of Q fever, which had become worse under treatment with sulfon-

amides and penicillin. With aureomycin, striking clinical improvement was apparent in 24 hours, and at the end of 48 hours the temperature was normal. Aureomycin, in a total dosage of 14.25 Gm., was given for 7 days. Progressive clearing of the pneumonic consolidation which had been present in the right upper and middle lobes was seen on serial X-rays. Convalescence was uneventful, and 1 month after the onset of the illness, the patient felt completely well, and his lungs appeared normal to X-ray.

Moeschlin and Koszewski<sup>216</sup> lay emphasis on the frequency with which complications may occur in the second to sixth week after the onset of Q fever, even when the fever itself has apparently been controlled by aureomycin or a similar antibiotic. Complications include thrombophlebitis, pulmonary embolism, epididymitis, encephalitis, pancreatitis and lymphocytic meningitis. They recommend that the patient convalescing from Q fever be not allowed to get up or to leave the hospital too soon, and that he should not be permitted to return to work until his temperature has been normal for 3 or 4 weeks.

Gsell<sup>114</sup> noted that in 9 cases given aureomycin with outstandingly good results, there were no complications; as compared to 3 cases of thrombophlebitis, 1 of meningitis, 2 of pleuritis, and 1 of fatal encephalitis, in 14 controls.

Since a pulmonary syndrome is predominant in Q fever, it would be of great practical interest to be able to make an early diagnosis by inspection of the sputum. Steinmann<sup>295</sup> states that he has been able to do so in 1 case, in which microscopic examination of the sputum permitted the diagnosis of Q fever 10 days before the results of agglutination tests were available. In the sputum of this patient, Steinmann found a certain number of macrophages, usually collected in colonies, in whose protoplasm there were granulations of irregular shape but of almost equal size, either polyhedral or in short filaments, and of a reddish violet color. Recognition of the typical morphology of these formations led to early effective therapy with aureomycin.

Coudert and Garin<sup>62</sup> gave aureomycin to 1 patient with Q fever with pneumonitis and hemoptysis, which had been unaffected by penicillin and sulfonamides. The temperature dropped to normal in 48 hours and the pulmonary signs disappeared in a week. Waldo<sup>313</sup> also observed benefit in 1 case.

Innerfield and Selmann<sup>144</sup> saw almost immediate clinical improvement in 2 patients with Q fever when aureomycin was given. They consider that the drug acted with gratifying speed and effectiveness to bring about the disappearance of all signs and symptoms of disease.

Meldolesi<sup>209</sup> states that the therapy of Q fever has become simple and effective with the introduction of aureomycin, which by itself influences the course of this malady in a decisive manner within 3 days of beginning treatment. In this space of time, there is evident improvement in the general condition and in the symptoms, a drop in the fever, and definite regression of objective signs. It becomes absolutely impossible to isolate the rickettsia from the blood, sputum, milk, or urine of the sick patient. In a very few cases of chronic or recurrent nature, a second course of treatment is necessary to produce final cure. He advocates the use of adrenal cortical extract and vitamin E for the long-drawn-out asthenia which follows many cases of Q fever. In difficult or complicated cases, as for example in patients with subacute pulmonary infiltration, aureomycin should be given as early as possible. In subacute cases with protracted illness, a single course of 8 Gm. of aureomycin may not be effective, and in such cases several such courses (with a few weeks' interval between) are necessary to obtain a clear-cut result.

## *Radiation Sickness*

After the systemic absorption of excessive amounts of radiation, severe damage to the animal develops and may result in death. The most pronounced derangement produced by large doses of



X-rays to the body is the development of a hemorrhagic diathesis, possibly with damage to important organs from extravasation of blood into or around them. Associated injury to the bone marrow produces panhematopenia, and injury to the reticuloendothelial system in general interferes with humoral antibody response to bacterial antigens. Bacterial infection then becomes an important element in producing morbidity and death. In experimental animals subjected to whole-body X-radiation by Furth and co-workers,<sup>97</sup> administration of aureomycin reduced the death rate, and postponed death in fatal cases. The authors believe that the changes which they have observed are related to the control of infection by aureomycin. The growth-promoting power of aureomycin may enter into this protective effect, and the authors believe that some of the protection may result from an antitoxic effect of aureomycin.

As a rule, septicemia develops in the second week after radiation injury. Other forms of damage, including leukopenia, also become evident at this time and the animal's nutritional and immunologic state is at a low level. In the septicemia of experimental animals, the causative organisms are those normally present in the colon and may produce an overwhelming sepsis. The special susceptibility of the intestinal mucosa to radiation injury permits early systemic invasion by the bacterial inhabitants of the gut.<sup>119,213</sup>

The Atomic Energy Commission, in its Ninth Semi-Annual Report,<sup>8</sup> noted the effectiveness of therapy with antibiotics of the type of aureomycin, in carrying experimental animals safely over the period of reduced resistance to infection. The use of aureomycin in the treatment of experimental radiation injury produces alleviation of diarrhea and prolongation of life in rats and lowers mortality in dogs.<sup>140</sup> When mice were irradiated, death occurred in 33 per cent of those treated, as compared with 83 per cent of the controls.<sup>213</sup>

Lambert and associates<sup>168</sup> have found that when rats were subjected to a total dose of 500 r, an amount of radiation which is

almost uniformly fatal in untreated animals, 17 of 24 rats treated with aureomycin were alive on the thirtieth day, but only 4 of 24 controls. With higher dosages (of the order of 600 r), this protective effect was no longer manifest.

Innerfield and Angrist<sup>143</sup> also found that aureomycin exerts some protective effect against the biologic destructiveness of radiation, if administered within 10 minutes before total body irradiation. In a small series of mice, the survival period, the morbidity, and mortality rates, as well as the hemotologic changes, were favorably influenced.

In radiation injury, the body becomes incapable of responding to injections designed to produce active immunization, and antibodies which are already present may deteriorate. Allen, Moulder and Enerson<sup>2,3</sup> suggest the injection of previously-formed antibodies, such as those contained in tetanus antitoxin, and the liberal use of antibiotic therapy in the treatment of radiation sickness. According to them, the use of antibiotics, and particularly of aureomycin, is the most effective method of combating infection and of prolonging life in irradiated dogs. Weight loss, weakness, anorexia, anemia and leukopenia are all later in developing. The drop in platelets is not affected. A combination of aureomycin therapy and blood transfusion permitted some dogs to survive radiation doses which were about 25 per cent higher than the usual lethal exposure.

While there is available no reliable evidence as to the best time for beginning prophylactic treatment in human cases of radiation injury, Cronkite<sup>65</sup> believes that oral administration of penicillin and aureomycin should be started at about the beginning of the second week. They should be given intensively, orally or parenterally, if there are clinical signs of infection. Antibiotics will help to prevent ulceration and massive fatal hemorrhage following erosion of blood vessels.

Arons and Freeman<sup>7</sup> gave aureomycin to 5 patients in whom radiation sickness and lymphopenia interfered with X-ray therapy

for malignant disease. In 1 patient with fever, epigastric pain, nausea and diarrhea, following irradiation of the stomach, intravenous aureomycin produced normal temperatures in 24 hours and relief of symptoms in 72 hours. The second patient, suffering from vomiting and diarrhea during irradiation of the lower abdomen, felt better less than 5 hours after the first intravenous injection and was able to finish treatment. The third patient, also receiving X-rays to the lower abdomen, developed pruritus and a papulocrythematosus eruption in the treated area. Itching was relieved by oral aureomycin in 24 hours and the skin was clear by the fourth day. Irradiation of the chest in a fourth patient, and of the cervix in a fifth, was followed by increasingly severe diarrhea, not controlled by the usual measures, including pyridoxine administration. In both cases, intravenous aureomycin halted the diarrhea within 4 days. Fever and an extremely foul vaginal discharge, present in the fifth patient after radiation, subsided within 48 hours.

Maisin<sup>104</sup> notes that if, at the time of an atomic explosion, the physician has no instrument to measure the order of intensity of the dose received by a patient, an extremely simple and fairly precise medical method may be used: the time of appearance of vomiting. All injured persons who vomit at once, or within the hour following the explosion, may be considered as having received a fatal dose. No particular care beyond the relief of pain and the provision of rest should be given them. Those who vomit later, 2 hours or more after the explosion, are capable of being saved and must be cared for actively and adequately. Those who have not vomited at all have no need of any treatment and should be sent home. Maisin goes on to remark that one of the principal causes of death is destruction of the bone marrow, with resultant leukopenia and susceptibility to infection; this infection having its major source in the digestive tube. He and his students have found that the best method of preventing infection through this portal is the disinfection of the intestine by sufficient doses of aureomycin.

This method has the advantage of guarding at the same time against infection coming by other routes; and the polyvalence of the antibiotic provides a safeguard not only against the great majority of likely pathogens but against some viruses. Another outstanding advantage of aureomycin is the fact that the patient may receive it at home. The author feels that the fight against infection is of the highest importance and should be commenced very early after atomic attack, so that disinfection of the intestinal system may be as perfect as possible. Protein therapy is second in importance only to antibiotic therapy. The best form is intravenous plasma or whole blood, but it is likely that there will be a grave deficiency of these materials after a catastrophe of this order. Abundant reserves of plasma should be laid aside long in advance. In the absence of blood or plasma, some other form of protein should be offered; amino acids such as LEDINAC\* Liver Protein Hydrolysate should prove very valuable. If the patient is not too nauseated, the ingestion of a very generous proportion of proteins in the diet may be sufficient. Maisin also recommends the use of aureomycin for the prevention of infection in the surface burns which follow atomic explosions.

### *Rat-bite Fever (Sodoku)*

Rat-bite fever has been successfully treated with aureomycin, after failure of penicillin and streptomycin.<sup>124,188</sup> Rat-bite fever may in reality be 2 or more diseases, since the symptoms and the response to treatment vary greatly, and at least 2 organisms have been isolated and considered to be responsible for rat-bite fever. These are *Streptobacillus moniliformis* and *Spirillum minus*.

Dolman and associates<sup>81</sup> have described 2 cases of rat-bite fever due to *S. moniliformis*, in Canada. The disease occurred in 2 girl cousins who lived in a home infested with rats, and who had both been bitten on the hand. One child was ambulatory throughout and showed a low-grade intermittent fever for about 11 weeks,

during most of which time she was in the hospital. The other child, more severely ill, was in the hospital for about 3 months. Both children at first had blood cultures positive for *S. moniliformis*, and both had later positive cultures for pleuropneumonia-like organisms, this observation lending support to the hypothesis that the latter organisms may be variants of the former. The pleuropneumonia ("L") organism is very resistant to penicillin; in both children, bacteremia persisted in spite of penicillin administration. Aureomycin, 1 Gm. daily, was given for 14 days, and after it had been begun, there were no positive blood cultures and the patients became free of symptoms.

Logan and co-workers<sup>185</sup> reported a severe chronic case of rat-bite fever, apparently of 4½ years' duration, in a child. In spite of more than 8 months of treatment with penicillin, streptomycin, mapharsen and sulfadiazine, there was no clinical improvement, and blood cultures remained positive for *Spirillum minus*. The condition responded to aureomycin. After 3 months without medication the patient remained asymptomatic, with negative blood culture.

Another very difficult case, observed by Karelitz,<sup>151</sup> was that of a seven-year-old boy, hospitalized for 3½ years. He was in extremely poor condition, with fever, positive blood culture for *Sp. minus*, hemiplegia, pansinusitis and otitis, bronchiectasis and indolent skin ulcers. The spirillum was resistant to penicillin and the child did not respond to mapharsen or streptomycin. Aureomycin rapidly eliminated the organism and healed the ulcers. The sinus and pulmonary infections were relieved but not cured. The patient returned sometime later, with pneumonia and bacteremia due to *H. influenzae b*, and recovered promptly on aureomycin therapy.

Steen<sup>293</sup> found aureomycin to be effective against a strain of *Streptobacillus moniliformis* (*Haverhillia multiformis*, *Streptothrix muris ratti*) isolated from the blood of a child with rat-bite fever, which developed 3 days after being bitten in the tongue by a wild

brown rat. The organism was resistant to sulfonamides, and susceptible to 0.03 units of penicillin per cc., 0.5 micrograms of aureomycin per cc. and 4.0 micrograms of streptomycin per cc.

Christiansen and Birge<sup>45</sup> refer to a case of infection with *Streptobacillus moniliformis*, which developed during streptomycin and penicillin therapy after removal of a gangrenous appendix. Drainage of a large subhepatic abscess and addition of aureomycin to the therapy brought the patient's temperature to normal within 24 hours. Recovery was prompt. *Strep. moniliformis* was cultured from the pus. Nine months after operation, the patient was still well.

Shwartzman and co-workers<sup>273</sup> have reported the repeated recovery of a spirillum similar to *Sp. minus* from the blood of 2 children with prolonged fever. One child who had no definite history of rat bite, had involvement of the skin, central nervous system, respiratory system and intestinal tract. This case proved fatal, after failure of treatment with arsenicals, penicillin and streptomycin. The other child had a history of rat bite 3½ years previously, had since had repeated respiratory infections, suffered from indolent skin ulcers, and was hemiplegic. No response occurred to penicillin and sulfarsphenamine and, although the organism was sensitive *in vitro* to streptomycin, which was able to produce negative blood cultures, several months' treatment with as much as 2 Gm. daily failed to improve the child's condition. When aureomycin was given, the blood stream became permanently sterilized, the ulcers healed and the child's condition improved remarkably. The difference in the clinical picture in the course of these 2 cases from that of classical rat-bite fever suggested to the authors that *Sp. minus*, when it does cause disease in man, produces a disease which is not rat-bite fever as it is known on the American continent. The illnesses of these children were not unlike Sodoku which, in its typical form, is contracted from the bite of a rat. The authors suggest the use of the term "Spirillum Fever" for this type of infection.

## Relapsing Fever

In acute *Borrelia duttoni* infection, aureomycin gives dramatic relief. The blood becomes free of treponemata after 1 or 2 doses,<sup>104,127,130,324</sup> and serologic tests become negative.<sup>324</sup> Gilchrist<sup>104</sup> has treated 4 adults and 4 children, all acutely ill, with rapid clearing of the treponema from the blood stream and return to normal temperatures in 6 to 14 hours.

Yeo,<sup>323,324</sup> reporting satisfactory results in 25 cases, noted that the relapse rate of 12 per cent was only about half that seen in series treated with other drugs. Of the 3 cases which relapsed, 1 was a comparatively severe case with hepatomegaly, jaundice and iritis, and 2 had received very insufficient treatment (1.0 Gm. and 1.5 Gm. of aureomycin, respectively).

Trowell<sup>306</sup> speaks of aureomycin as the specific therapeutic agent for relapsing fever. It is extremely effective in very small doses for control of the fever and spirochetemia, and apparently considerably decreases, if it does not altogether abolish, the incidence of relapse. One to 2 Gm. will probably bring about complete cure in most cases. At least a third of the cases of tick-borne relapsing fever treated by arsenicals or penicillin will relapse within 7 days, and about half in 10 to 20 days. During 1950, he treated 14 patients with relapsing fever, with aureomycin. A control group contained 13 cases, but 2 of these, both children, were so seriously ill, with repeated relapses, that they were transferred to the aureomycin-treated group. Eight of the control cases were known to have relapses and there was 1 death from hepatitis in this group. In the treated group there were no relapses. The mean duration of the febrile period, after the blood smear had been found positive and aureomycin commenced, was 11 hours; within 3 hours of the first dose, the spirochetes had usually disappeared. Two additional cases were treated with aureomycin, but were not included in the above group because the blood smear was never positive. However, the complement-fixation test showed that the patients had been suf-

fering from relapsing fever. One patient had a severe myelitis, and the other had a meningoencephalitis and iridocyclitis, and both had experienced several bouts of fever. They improved very rapidly under aureomycin administration. An additional 2 cases were detected after the close of this study, and appeared to be clinically cured after taking only 0.5 Gm. of aureomycin. The blood smear became negative in both cases, within 2 hours of administration of the first dose, and no relapse was observed in the next 8 and 10 days.

Innerfield<sup>142</sup> has reported recovery in a case of relapsing fever with positive blood culture, for which aureomycin was the only therapeutic agent used. Remarkable symptomatic improvement was observed by the eighteenth hour of treatment, and the temperature was normal on the tenth day. Joint and muscle pains soon disappeared, the palpable spleen rapidly decreased in size, and blood cultures became permanently negative on the third day of treatment. A similar attack, occurring about a year previously, had lasted for more than 5 weeks.

In 2 cases of recurrent fever produced by *B. turicata*, Mazzotti<sup>204</sup> found aureomycin to be effective. Blood cultures became permanently negative within 5 hours in 1 patient and within 24 hours in the other. Supportive measures are important for obtaining the most rapid and satisfactory cure of borrelia infection.<sup>130</sup>

## *Rheumatic Disease*

Brown and co-workers<sup>32</sup> have presented evidence to indicate the existence of hypersensitivity as a factor in the production of rheumatic disease. The action of cortisone and ACTH appears to be a blocking of the antigen-antibody reaction, without any effect on the antigen itself. These authors have found evidence that in some cases more antigen may be released by antibiotics, thus producing a flare-up of the rheumatic condition. Most patients treated with aureomycin, however, have shown definite clinical improvement. Relapse is frequent after the drug is stopped, but can be controlled



by further treatment. In those cases in which exacerbation was produced by aureomycin, ultimate clinical improvement was obtained by intermittent administration, giving small doses every 3 days, and slowly increasing each dose to the limit of tolerance. Combined treatment with cortisone and antibiotic permitted the tolerance to be raised to a greater degree and with greater speed than when the antibiotic alone was used.

There are indications that the antigen is a living organism, of extremely minute size and able to evoke intense antibody production. Its relation to the organisms, such as streptococcus, gonococcus and streptobacillus, which are usually associated with joint involvement, awaits clarification.

Mankle and Kuzell<sup>196</sup> point out that the beneficial effect of gold salts and of tetrathiodiglycolic acid, in rheumatoid arthritis, has been thought to result from their binding of free sulfhydryl groups. Glutathione and BAL, when fed to rats suffering from arthritis induced by infection with pleuropneumonia-like organisms, produce aggravation of the condition; these 2 agents contain sulfhydryl groups.

The observation of Tzanck and co-workers<sup>307</sup> that aureomycin produces a remarkable fall in the sulfhydryl content of the dermal cells in certain skin infections, and that it is able to bring about total blockage of SH groups, suggests that the known effectiveness of aureomycin in rheumatic disease is based upon this type of reaction.

In a study by Ludwig and Murray,<sup>191</sup> aureomycin (but not terramycin or chloramphenicol) was shown to offer protection against arthritis in rats experimentally infected with the L<sub>4</sub> strain of pleuropneumonia-like organisms.

Chura and his colleagues<sup>47</sup> gave aureomycin as the sole treatment, (5 to 22 Gm. in 9 to 20 days) to 21 children with acute rheumatism, all having cardiac involvement and most of them gravely ill. Psychic changes were evident. The effect of aureomycin was remarkable. In 5 to 11 days, each child regained the mental and physical activity proper to his age. Cardiac murmurs decreased

in intensity or disappeared entirely. The area of cardiac dullness returned to normal and pericarditis cleared. The sedimentation rate reached a normal level. If the dose of aureomycin was reduced or stopped too early, some manifestations of the disease reappeared. The authors advise continuing aureomycin administration for at least 14 days after apparent cure, in mild cases, and for at least 21 days in all others. It is necessary to differentiate between the primary attack of rheumatic fever and a recurrence, since cure with aureomycin is more certain in the former.

### *Rickettsial Infection*

The status of the rickettsial infections has radically changed since the advent of aureomycin.<sup>280</sup> The dramatic results obtained by its use contrast strongly with the lack of any specific response to earlier methods of treatment. Since aureomycin acts mainly as a rickettsiostatic agent, full recovery depends on the development of immunity by the patient. Early treatment may interfere with the development of an immune response and seriously interfere with diagnosis. Relapse will occur if the antibiotic is discontinued before an adequate immune state has been attained. Smadel<sup>280</sup> believes that, in the absence of a simple specific diagnostic test, therapeutic antibiotic trial may be of value, and that chemoprophylaxis may be useful for the prevention of rickettsial disease when the proper vaccine is not available.

Höring<sup>138</sup> has suggested that in view of the apparently bacteriostatic action of aureomycin, it may be possible to immunize patients against rickettsial disease by exposing them, under antibiotic protection, so that they will contract a subclinical form of the disease.

### *Rickettsialpox*

Rickettsialpox is neither a common nor a commonly diagnosed disease; but enough reports are available to indicate that aureo-

mycin is effective in it, as in other rickettsial infections. Rose, Kneeland and Gibson<sup>252,253</sup> have reported a series of 8 cases of rickettsialpox, treated with aureomycin with uniformly rapid and favorable therapeutic results. They consider that rickettsialpox may be added to the other rickettsial infections in which the effect of aureomycin is promptly curative. While the disease is not serious, it incapacitates the patient for some time and makes him severely uncomfortable for several days. They therefore suggest that treatment with this antibiotic be considered whenever the diagnosis appears reasonably certain. The authors point out that the high antibody titer usually found during convalescence from rickettsialpox did not appear in their aureomycin-treated patients, and attribute this fact to the prompt and complete suppression of rickettsial multiplication by aureomycin, so that insufficient antigenic stimulus was provided for immunologic response.

### *Rocky Mountain Spotted Fever*

Rocky Mountain spotted fever, a very severe acute infectious disease produced by *R. rickettsii*, with a high mortality rate, is apparently spreading more and more widely over the northern hemisphere. Penicillin and streptomycin are inactive against the organisms, and sulfonamides appear to intensify the severity of the disease. Aureomycin, which attacks the rickettsiae within the body cells themselves, is superior to any previous remedy, including para-aminobenzoic acid. Early treatment does not, as a rule, interfere with the production of diagnostic antibodies.<sup>219</sup> The prognosis is good for the average attack, if treatment is begun within a week of onset, and is fair in even the most severe cases. A large number of Rocky Mountain spotted fever patients have been successfully treated with aureomycin.<sup>11,25,57,82,83,121,124,126,129,131,219,247,256</sup>

Prompt recovery almost invariably follows the administration of therapeutically effective doses of aureomycin.<sup>131</sup> Improvement begins within 24 to 48 hours of the first dose of aureomycin and

the patient is usually convalescent in a few days. Even in very severe cases, normal temperatures are usually reached within 24 to 48 hours. These results are all the more striking, since the over-all mortality rate previous to this newer form of therapy has been in the neighborhood of 25 per cent, with a prognosis which is increasingly poor in patients over 40 years of age.

Arney<sup>5</sup> has reported remarkable response to cortisone and aureomycin in a severely toxic case of Rocky Mountain spotted fever. The patient on admission was restless, confused and semi-stuporous and, in spite of chloramphenicol and supportive intravenous therapy, went steadily downhill. At the time when the aureomycin-cortisone treatment was decided upon, the patient was obviously near death, was comatose, and was unable to take anything by mouth. Inside of 6 hours after beginning the new treatment, she was improving; after 18 hours, she was again able to drink; after 24 hours, her temperature remained normal, and subsequent convalescence was uninterrupted.

Harrell<sup>131</sup> believes that, except for the possible requirement of oxygen by seriously ill patients, no other treatment except supportive measures is required when aureomycin is used. He refers to Harrell's observation that the prognosis of spotted fever is greatly improved if the patient has been vaccinated within a year. Not only is mortality reduced but the clinical severity and duration of the illness is also lessened.

Harrell<sup>120</sup> states that early treatment is so important for the prevention of complications in Rocky Mountain spotted fever that it may be wiser to administer aureomycin on mere suspicion of the disease, and suggests that a combination of aureomycin and PABA may prove more effective than either alone.

## *Scarlet Fever*

Scarlet fever is now more generally referred to as streptococcal sore throat with rash. It has been found to yield to aureomycin

rapidly and without complications.<sup>82,92,124</sup> Even though penicillin is still the drug of choice in beta-hemolytic streptococcal infections, there are enough patients who are sensitive to penicillin to make it advisable to evaluate the effects of aureomycin in this type of infection. Dowling and co-workers<sup>82</sup> treated 9 patients with scarlet fever, and all returned to normal temperatures soon after beginning aureomycin. Recovery was free from complications. One patient with cellulitis and 1 with bacteremia, also caused by beta-hemolytic streptococci, recovered within 24 hours. Three patients with upper respiratory beta-hemolytic streptococcus infections, reported by Finland and co-workers,<sup>92</sup> showed marked symptomatic improvement and return to normal temperatures, 12 to 24 hours after the first dose of aureomycin.

Bender<sup>15</sup> advocates a prophylactic period of isolation, with continued administration of aureomycin for 8 or 10 days, in streptococcal infections, such as scarlet fever, which end by crisis soon after beginning the antibiotic. These patients are particularly prone to reinfection.

Breese<sup>30</sup> has given aureomycin to 50 children with beta-hemolytic streptococcal infections, some of them having had more than 1 attack. There were 51 attacks of streptococcal sore throat, 3 of scarlet fever, 2 of cervical adenitis, 3 of otitis media, 1 of vaginitis. Four children were asymptomatic carriers. The children were treated at home and, as a rule, aureomycin was given in a dosage of 5 mg. per kilo for 24 hours, calculated to the nearest 50 mg. After 2 to 5 days, the dose was halved and continued for a total period of 4 to 12 days. All cases responded well, the patient usually becoming afebrile and asymptomatic within 24 hours. In no case, except those with suppurative lesions, did cure take longer than 48 hours. There were no relapses or complications during aureomycin treatment. After 48 hours of treatment, all cultures became negative; but there were 12 clinical recurrences and 7 asymptomatic bacteriologic recurrences, after treatment was stopped. No serious late complications, such as are often

associated with streptococcal infection, were observed.

With modern antibiotics, the death rate from scarlet fever and erysipelas has now, according to Long,<sup>187</sup> been reduced practically to zero.

## *Scrub Typhus*

Uncomplicated, untreated cases of scrub typhus generally run a course of 14 days, the fever dropping by lysis about the end of the second week. The immune mechanism apparently begins to become effective towards the middle of that week, and to gain the upper hand of the infection by the fourteenth day. Aureomycin is effective against the causative organism, *Rickettsia tsutsugamushi*.<sup>300,318</sup>

Smadel's group,<sup>281</sup> studying the response of infected volunteers to aureomycin, found that the disease could be promptly arrested by it. Relapses occur when the disease is treated in the first few days; but can be either terminated by a second course of treatment, or prevented by a supplemental dose of the antibiotic, given on the eighth or ninth day after onset. Since all of the broad-spectrum antibiotics are rickettsiostatic and not bactericidal, recurrences are inevitable if the infection is arrested by them before immunity has developed. These authors<sup>10</sup> obtained satisfactory results with aureomycin in 30 patients with scrub typhus, and in 4 who were unable to continue with terramycin therapy on account of vomiting. The response to aureomycin or to chloramphenicol was in general more promptly satisfactory than was that to terramycin. If antibiotics were begun during the second week of illness, the patient had apparently developed enough immunity before treatment was completed to prevent the development of relapse.

Smadel<sup>279</sup> has studied the effect of various antibiotics in scrub typhus patients in Malaya, where the mortality is about 5 per cent. One hundred patients were given chloramphenicol, and the duration of fever after beginning treatment was an average of 31 hours; 29 patients were given aureomycin, and the average duration of

fever was 25 hours; 7 patients given terramycin were afebrile after an average of 47 hours; 15 patients treated with para-aminobenzoic acid were not afebrile until almost 90 hours after the drug had been started. In 19 untreated control patients, the average duration of fever was 17 days. There were no deaths in the 151 treated cases, and 1 death in the 19 controls.

Krishnan and co-workers<sup>166</sup> have reported satisfactory results in 3 cases of scrub typhus treated with aureomycin. In every case the patient was afebrile within 48 hours and the other symptoms had disappeared in a few days, including those referable to the nervous system. One of the 3 cases thus treated was of the severe type, in which the mortality is usually about 10 per cent.

Two cases of scrub typhus, contracted in Korea, have been reported by the Royal Army Medical Corps.<sup>221</sup> One patient was given chloramphenicol at once, as soon as the tentative diagnosis of scrub typhus was made; but 2 days later, although the temperature had fallen almost to normal, the blood pressure was very low, bronchopneumonia was present and the patient seemed to have carditis. Aureomycin was given, as well as chloramphenicol, and the next day he was afebrile and remained so. The pneumonia cleared rapidly and 2 days later the blood pressure was almost normal. The second patient suffered from great muscular weakness and some mental confusion, and had carditis. He also was given aureomycin and chloramphenicol and recovered slowly but satisfactorily.

## *Septicemia*

The proven effectiveness of aureomycin against a very wide range of organisms, embracing both Gram-positive and Gram-negative cocci and bacilli, spirochetes, rickettsiae, and certain of the large viruses and of the protozoa, indicates its usefulness in blood stream invasion by these organisms, a usefulness which has been repeatedly demonstrated in the past 5 years.<sup>25,53,82,189,206,242,288,326</sup>

At the 1951 meeting of the American College of Physicians,<sup>1</sup> it was stated that in infection by either streptococcus or staphylococcus, aureomycin was better than penicillin.

In Friedländer bacillus infections, either streptomycin or aureomycin is the drug to be chosen.<sup>155</sup>

Faggioli<sup>87</sup> has found that *Klebsiella ozenae* or *pneumoniae* can develop forms which are not only resistant to streptomycin and to chloramphenicol but which are actually dependent upon these antibiotics. Attempts to demonstrate a similar effect with aureomycin had no result.

McVay and Sprunt<sup>208</sup> are of the opinion that *Bacteroides* infection occurs more frequently than the medical literature would indicate. They suggest that the pathogen may often be overlooked unless anaerobic cultures are made. These organisms are normal inhabitants of the feces, but may enter the blood stream, particularly after surgery of the intestinal and urinary tracts. Many dangerous septicemias of unknown etiology may be caused by this organism. If untreated or inadequately treated, bacteroides infections are often fatal, and usually prolonged and debilitating. The authors have found, both *in vitro* and clinically, that aureomycin is the most effective remedy against this organism. When it cannot be given orally, it should be given intravenously. In view of the chronic course often taken, maintenance of nutrition and of fluid and electrolyte balance, and indicated surgery, are important in improving the resistance of the patient.

Aureomycin was effective in one case of septicemia due to *Bacteroides funduliformis*.<sup>54</sup> Before aureomycin, the prognosis would have been extremely poor.

Ramsay and Vahrman<sup>243</sup> recommend that massive doses of penicillin be used in cases of staphylococcal septicemia, to provide adequate penetration into pyemic abscesses and to prevent the development of penicillin-resistant strains. If clinical benefit does not follow within 48 hours, recourse to aureomycin is advised.

Julsrud<sup>148</sup> also advises the use of aureomycin in septicemia due



to infection with penicillin-resistant staphylococci. He quotes 2 cases in which cure followed treatment with streptomycin and aureomycin, after failure of penicillin.

In 2 cases of *Staph. albus* septicemia resistant to penicillin, reported by Levinson and co-workers,<sup>177</sup> aureomycin brought about cure.

The death rate in untreated staphylococcal bacteremia is between 75 and 80 per cent. In this condition aureomycin is probably the drug of choice, particularly when the organism is penicillin-resistant.<sup>224</sup> Temperatures usually return to normal within a few days, with sterile blood cultures after the first 24 hours. Finland and associates<sup>91</sup> report that, *in vitro*, aureomycin was found to be the most active against staphylococci, of 7 antibiotics tested. Yow<sup>326</sup> found it to be effective in 5 cases of staphylococcal bacteremia failing to respond satisfactorily to a sulfonamide, penicillin and streptomycin, and feels that it may prove to be the drug of choice in severe staphylococcal infections. A patient with staphylococcal septicemia, secondary to furunculosis, was given penicillin and streptomycin without effect, by Martin and co-workers.<sup>199</sup> Tests proved later that the organism was resistant to both antibiotics, and cure was brought about by aureomycin.

Some strains of staphylococcus produce penicillinase, and thus oppose the action of penicillin, even though the organisms themselves may be sensitive. Martin and associates,<sup>198</sup> who have themselves observed this property of the staphylococcus, believe that, in the majority of cases in which greatly increased resistance to penicillin is apparent, elaboration of penicillinase forms the basis of this phenomenon.

Arnold<sup>6</sup> reports a child with severe agranulocytosis, cured by aureomycin which controlled a complicating *Staph. aureus hemolyticus* septicemia. Improvement was noted within 36 hours, and normal temperatures were reached within 78 hours. Aureomycin was continued for 2 weeks after the last positive blood culture, which was obtained on the fifth day of treatment. The granulo-

cytes increased within 7 days from 0% of 2,560 wbc to 88% of 16,000 wbc.

Dana and co-workers<sup>70</sup> have reported the case of a young man, who had suffered from staphylococemia for nearly a month. The illness began with a furuncle on the forearm and, at the time when he was first seen, the patient had a large subscapular abscess. After 1 month on the surgical service, the patient was transferred to the medical service in a state of advanced cachexia, reminding the observer of the conditions met with in concentration camps. The patient was unable to stand, and his color indicated his intense anemia (1,800,000 rbc). At this time there was also an extensive gangrenous abscess of the left coxofemoral region. Intensive treatment was begun with penicillin, streptomycin, a sulfonamide, bacitracin and antigangrene serum, associated with blood transfusions and large doses of vitamins B, B<sub>12</sub> and C. The general condition improved somewhat but there was no change in the gangrenous abscess. Aureomycin was then added to the previous remedies, and this addition was followed by local and general improvement. The patient began to be able to move his left hip. After 35 Gm. had been given, aureomycin was stopped, and 48 hours later a septic type of fever appeared. Treatment was recommenced, but when an attempt was once more made to stop it, the infectious syndrome returned. It was then decided to use aureomycin only, in a dose of 2 Gm. daily. In the succeeding 2 months of treatment, all symptoms improved very rapidly and the patient put on weight. For the next 2 months, after stopping treatment, the patient improved steadily and was able to walk more easily. At the end of this time, another attack of fever forced the physicians to prescribe aureomycin for an additional month. At the end of this time, the patient appeared to be completely cured, he could walk normally and his general condition was satisfactory. However, 6 weeks later, he had another attack of fever, which was treated by a fourth course of aureomycin, associated this time with vaccine therapy. This final treatment appeared to bring about complete cure. X-rays of the

left hip showed complete disappearance of the abscess. At the time of reporting this case, the patient had been well for more than a year.

*Micrococcus tetragenus* septicemia, which in the pre-antibiotic era carried a mortality of 50 per cent, has been successfully treated with aureomycin by Rambach.<sup>242</sup> The infection occurred in an anemic, undernourished, seven-year-old boy with a history of repeated episodes of otitis. No response was obtained to penicillin and supportive measures, nor to dihydrostreptomycin, nor to intravenous medication with penicillin and a sulfonamide, together with blood transfusion. Three weeks after admission, the blood cultures which had been negative showed growth of *Micr. tetragenus*, and this was confirmed by culture of the sternal marrow and of the urine. Fever persisted and signs of meningeal irritation appeared. Aureomycin therapy was instituted after 2 months of illness, and normal temperatures were reached in 48 hours. With the exception of 3 rises to 100.5° to 102° F., there was no return of fever and the patient was discharged about 3 weeks later. Follow-up studies after 2 months showed return to full activity, with gain in weight and appetite, and disappearance of urinary infection.

Copping and Reed<sup>59</sup> have presented a case of *Salmonella sandiego* septicemia, the first proven instance of this type of infection in Canada. The patient, an elderly man, suffered from diarrhea, headache and fever. Pyuria and hematuria developed and an incomplete prostatic obstruction progressed to complete closure. The patient was somewhat confused and his abdomen was distended: the illness resembled typhoid. Large dosage of penicillin had no noticeable effect on the condition. Penicillin was stopped on the fourteenth day of illness and, in view of the patient's age and his increasing toxicity, aureomycin and chloramphenicol were given in combination.

The diarrhea decreased and on the fourth day of this combined treatment, the temperature became normal and the patient was much improved. Phlebitis, which had developed on the first day of treatment, slowly subsided. Blood cultures were negative on

and after the second day of treatment. During antibiotic treatment, the stool and urine cultures remained negative, but as soon as the antibiotics were stopped, positive cultures were again obtained. Permanent negativity of stool and urine was not obtained until 17 weeks after the onset of the disease.

## *Smallpox*

As is to be expected, few opportunities of evaluating the effectiveness of modern therapy in smallpox present themselves in countries where vaccination is a routine procedure. Only now are reports on the use of aureomycin in this disease beginning to appear in the world literature.

In the winter of 1949-1950, epidemic smallpox broke out in Saudi Arabia, during the Mecca Pilgrimage, and was finally halted by mass vaccination. Corkill<sup>61</sup> reports that in the town of Jiddah alone, there were about 1,000 cases, of whom about 58 per cent died. In 35 severe unvaccinated cases, treated with penicillin and streptomycin, the death rate was 45 per cent. Five severe unvaccinated cases were treated with aureomycin. Only enough of the antibiotic was available to provide 2 or 3 days' treatment, and penicillin and streptomycin were used during the remainder of the illness. There was 1 death. Mental confusion developed in 3 of the 4 survivors, but cleared when treatment was stopped. The illness seemed to have an unusually smooth course.

While insufficient data are available for determining the precise effect of aureomycin on the virus of variola, it undoubtedly acts on secondary invaders to lessen toxicity and prevent complications. Wickham<sup>316</sup> has reported recovery in 1 very severe case of confluent smallpox with extensive nose and throat lesions, treated with penicillin and aureomycin. The evolution and duration of the disease was little changed, but no complication developed and the patient was on the way to recovery by the fifteenth day. Marsden and Coughlin<sup>197</sup> also observed no effect on the course of the virus

invasion in 5 cases of confluent hemorrhagic smallpox, 3 treated with aureomycin and 2 with chloramphenicol. Suppuration and odor did not develop, but all were severely toxic and death followed from exhaustion or heart failure.

Breen<sup>29</sup> treated 6 cases of smallpox, 3 of them fatal, with antibiotics; aureomycin, penicillin, chloramphenicol, again without any apparent effect on the virus. However, the unaffected skin remained healthy, there was no sepsis, and complications did not develop. Antibiosis undoubtedly aids in the body defense against secondary invaders, but this is rarely the deciding factor.

### *Tick-bite Fever*

South African tick-bite fever, caused by *Rickettsia rickettsii* var. *pijperi*, and tick typhus, occurring in Queensland, Australia, belong to an indefinite group of tick-borne rickettsial diseases, closely allied to "fièvre boutonneuse" and until recent years usually reported as "typhus fever." These diseases bear a close relation to the tick-borne fever better known to physicians on the North American continent as Rocky Mountain spotted fever.

The earliest reports on the use of aureomycin in South African tick-bite fever dealt with 3 cases treated in 1949,<sup>101,135</sup> with resultant rapid recovery. In 1 case, there was disappearance of fever within 14 hours and of all symptoms within 24 hours. This patient had been ill for a week previously but, within 72 hours after beginning treatment, he was able to return to work.<sup>135</sup> Less than a year later, Gear<sup>100</sup> reported that the results of aureomycin treatment had been excellent in 30 cases of tick-bite fever. Normal temperatures were attained in 48 hours and there were no relapses. He considers the drug a specific in this infection. Given at the time of the primary sore, it will abort the attack.

In 8 aureomycin-treated cases of tick typhus reported by Henderson and co-workers,<sup>128</sup> the patient was afebrile in 72 hours on the average. There were 11 deaths among 400 cases of tick typhus

treated in the Tata Main Hospital, Jamshedpur, India, but none in 20 cases treated with aureomycin.<sup>158</sup>

Cluver<sup>51</sup> has described dramatic response to aureomycin in 1 case of severe tick typhus fever, with enlarged glands and inguinal buboes. The rapid control of infection by aureomycin appears to eliminate any risk of persistent tachycardia.<sup>128</sup>

## *Toxoplasmosis*

In early toxoplasmosis, aureomycin seems to have some curative effect, and alters the serologic titer.<sup>314</sup> In the very early stages, acute toxoplasmosis is susceptible to treatment with various sulfonamides and antibiotics, including aureomycin, as has been found by Steen<sup>292</sup> in experimental toxoplasmosis in mice.

It is possible that no adequate treatment will be found for clinical toxoplasmosis in man, since the diagnosis can only be made after symptoms have become manifest, at which time the disease is no longer responsive to treatment.<sup>95,301</sup>

In 5 cases of ocular toxoplasmosis given aureomycin by Straub,<sup>298</sup> preliminary results were apparently favorable.

Campbell and Clifton<sup>38</sup> emphasize that there is a familial aspect to toxoplasmosis, and that in adult cases a modified picture may be seen. In young children, 1 or more of a triad of symptoms may be found: hydrocephalus, choroidoretinitis and cerebral calcification. Immune bodies may be found in the patient's serum, but demonstration of the organism itself is very difficult. They describe one family in which there was evidence of transmission of toxoplasmosis through 3 generations. The disease was, at the time of writing, subacute in at least 3 and possibly 4 members of the family, who had suffered from chronic ill health for many years. Some response has been noted to sulfonamides, but other drugs including the available antibiotics have had little action, at least in patients with clinical evidence of the disease.

A case reported by Hartl<sup>123</sup> suggests that it may be possible to

prevent congenital toxoplasmosis by the administration of oral aureomycin to the mother, since passage of aureomycin into the fetal circulation should provide protection for the child. He based this opinion on the case of a woman suffering from severe anemia after an abortion, who was found to have had 3 previous miscarriages or premature births due to latent toxoplasmosis. After 4 Gm. of aureomycin, the Sabin-Feldman test became negative. The outcome of future pregnancies in this patient will be watched with interest.

## *Tuberculosis*

The therapeutic effect of any agent on a disease process is dependent on the ability of the drug to reach the lesion. In tuberculosis, aureomycin is not carried in sufficient concentration into caseous lesions, and cannot sterilize lymph nodes. It does, however, sterilize the periphery of the node or abscess, and has a definite healing action on draining sinuses. Cordice, Hill and Wright<sup>60</sup> have used aureomycin in the treatment of 25 patients with tuberculous regional lymphadenitis, abscesses, and sinuses. Surgery was employed when indicated. In a number of cases, aureomycin exerted a definite effect on the progress of the infection. It seemed to slow or halt the disease process and to hinder the development of abscesses and sinuses, although renewed activity may follow cessation of treatment. That aureomycin does have a clinical tuberculostatic effect is indicated by the fact that in 2 of the successfully treated sinuses, no organism other than *M. tuberculosis* could be found on smear or culture. Two important advantages in the use of aureomycin are the low toxicity of the drug and the failure of resistant organisms to appear. It appears to be particularly useful as an adjunct to adequate surgery.

Long<sup>186</sup> has mentioned a patient with advanced tuberculosis of the urinary tract and marked bladder involvement, who had undergone lobectomy because of tuberculosis. While under treatment

for 2 months with aureomycin, the patient showed marked remission of signs and symptoms.

Schoenbach and his colleagues<sup>264</sup> gave aureomycin to a twelve-year-old girl with draining tuberculous sinuses in her neck, which had been present for 5 years. On aureomycin treatment all sinuses closed within 10 days. The antibiotic was continued for 7 weeks, and 6 months later there had been no recurrence.<sup>265</sup>

In view of the profound alterations which he has observed aureomycin to produce in the growth, morphology and physiology of *M. tuberculosis*, Sirsi<sup>278</sup> suggests that aureomycin may be useful, combined with other tuberculostatic agents, for the treatment of tuberculosis, and is at present studying the synergistic action of aureomycin with such agents. He has himself observed a patient who was given aureomycin for what was thought to be atypical pneumonia. The fever subsided; a week later it relapsed, and another course of aureomycin again brought down the temperature. Sputum examinations meanwhile revealed *M. tuberculosis*. He points to this case as indication that aureomycin does have some effect in controlling the disease.

## Tularemia

Aureomycin is distinctly effective *in vitro* and *in vivo* against *Pasteurellae*, including *multocida*,<sup>108,222,223</sup> *tularensis* and *pestis*.<sup>167,239,241,254,282</sup>

Depending on the portal of entry, tularemia may take a variety of forms: ulceroglandular (most common), glandular, oculoglandular, typhoidal, and gastrointestinal. The last 2 types are usually severe and death may follow rapidly, preceded by convulsions and coma. The central nervous system may be attacked by *P. tularensis*, but, as a rule, complications are caused by secondary invaders. Until streptomycin was introduced, there was no specific treatment, the sulfonamides and the previously known antibiotics being of no value.



Rosenthal<sup>256</sup> states that since aureomycin is more effective than streptomycin in mouse tularemia and, in the human cases in which it has been tried, it may become the drug of choice in this disease, a statement in which Long and his colleagues concur.<sup>188</sup>

The experience of Carroll and Gorman<sup>40</sup> with 1 patient indicates the superior effectiveness of aureomycin. During 10 days of streptomycin therapy, only slight subjective improvement had occurred. The day following the institution of aureomycin therapy, the patient felt decidedly better, and the temperature dropped to normal within 36 hours.

Woodward<sup>318,321</sup> reported marked reduction in toxemia and cough within 24 hours in 3 serious cases, with increase in strength and appetite, and prompt recovery. One was of the ulceroglandular and 2 were of the typhoidal variety. Similar results were obtained by Ransmeier, Price and Barnes<sup>244</sup> in 1 case of severe tularemic pneumonia and in 1 patient acutely ill with the ulceroglandular form of the disease and marked sepsis. Rapid response to aureomycin within 24 hours was observed in both. A third case also responded well, but suppuration occurred in an axillary node.

The rare oculoglandular form of tularemia responds to aureomycin with the same promptness as do the commoner varieties. Lindeke and Maiden<sup>181</sup> have reported what is apparently the first case treated with this antibiotic. The patient had failed to respond to penicillin and, on admission, was acutely ill, with a temperature of 102° F., swelling and tenderness of the right eye, edema of both lids, beefy hypertrophy of the palpebral conjunctivae, and discrete multiple ulcers of the palpebral conjunctiva of the right eye. There was pronounced chemosis of the bulbar conjunctiva, with superficial corneal opacities. On the third day, treatment was begun with oral aureomycin and local aureomycin ophthalmic solution. All the manifestations improved within 24 hours and the temperature became normal in 12 hours. One week later, there were only very slight residual manifestations, which disappeared within the next month.

Pesme and Dupin<sup>232</sup> have reported a case of ocular tularemia in

a fifteen-year-old boy, who was cured within a week by the use of streptomycin and local aureomycin, although convalescence was slow and marked by severe asthenia.

Taylor<sup>302</sup> reported the successful use of aureomycin in 2 cases. One was of the pneumonic type, with massive pleural effusion and probable pericarditis. The patient became rapidly worse on streptomycin and developed congestive heart failure. Following digitalization and unsuccessful thoracentesis, aureomycin was started. Marked improvement was visible inside of 24 hours, and was followed by cure. In the other case, one of ulceroglandular tularemia, the patient was dehydrated and stuporous on admission, but recovered rapidly on aureomycin treatment.

Dagradi and co-workers<sup>69</sup> observed dramatic subjective improvement within 2 days in a case of ulceroglandular tularemia. The temperature remained normal after 96 hours.

Tularemia may be carried, not only by infected ticks, but also by a secondarily infected animal. For example, Cinelli<sup>48</sup> mentions a case of ulceroglandular tularemia following a dog bite, noting that aureomycin gives brilliant results in tularemia and that it is one of the drugs of choice. That infection can also be transmitted without direct contact with either animals or arthropods is shown by Lindsay and Scott,<sup>182</sup> who describe the contracting of tularemia by a sewer worker into whose eye some of the sewage was spilled. On the following day, the disease made its appearance. The eye condition improved, and the fever disappeared, on treatment with streptomycin and aureomycin, and irradiation of the involved areas.

Robertson and associates<sup>250</sup> reported the aureomycin treatment of 2 patients with ulceroglandular tularemia. In 1 patient given aureomycin, plus penicillin for secondary infection, there was remarkable improvement within 48 hours, at which time the temperature had returned to normal and the lymphangitis had decreased. In 72 hours the patient was clinically well, except for a healing ulceration at the original site of infection. He was discharged on the sixth day. The second patient was treated at home

with aureomycin. Within 36 hours the temperature had fallen from 103° F. to normal, and symptoms gradually subsided.

In a case of glandular tularemia reported by Wimberley,<sup>317</sup> aureomycin, instituted on the second day of illness, controlled the symptoms within 24 hours. Signs of infection recurred when aureomycin was stopped, probably because insufficient time was given to permit the action of immune mechanisms. Further treatment with aureomycin brought about symptomatic cure, without relapse, within 24 hours. Wimberley considers aureomycin the drug of choice for the treatment of acute tularemia.

Poulet<sup>238</sup> advises the use of aureomycin in the treatment of tularemia, with streptomycin as a second choice. He notes that the skin test with killed *P. tularensis* becomes positive earlier than the serologic tests.

At the 1951 meeting of the American College of Physicians,<sup>1</sup> it was recommended that streptomycin and aureomycin be given together for tularemia; and that the disease be allowed to progress a few days before starting treatment, as otherwise the development of immunity might be hindered and expose the patient to the danger of relapse.

## *Typhoid Fever*

A number of authors have written on the apparent synergism between aureomycin and chloramphenicol in typhoid fever, reporting the curative effects of this combination in severe, complicated cases and advocating its use for gravely ill patients.<sup>17,18,249</sup>

Leypold<sup>178</sup> believes that, while chloramphenicol is the preferred drug for the treatment of typhoid fever, aureomycin has a very definite place. He has used the former in 10 cases and the latter in 5 cases of typhoid and paratyphoid, and states that the effect on the temperature produced by both antibiotics is something to be wondered at, in a disease which is so difficult to influence. Reduction in toxicity, clearing of the sensorium, return of appetite, all followed antibiotic treatment. No relapse occurred in any of the

15 patients. Disappearance of fever was not accompanied by a state of collapse, as is so often reported in the literature. He believes this to be accounted for by the rather slow reduction in temperature, consequent on the small amounts of antibiotic available at that time for treatment. Death occurred in 2 of the patients treated with aureomycin, 1 of them having an extremely severe toxic condition and the other being subjected to an emergency operation for perforated stomach ulcer.

Debray and co-workers<sup>73</sup> note that the addition of aureomycin to chloramphenicol seemed to have a favorable influence upon the course of typhoid encephalitis in 1 case. They believe that certain advantages are attached to the use of TAB vaccine in progressive doses, in an effort to diminish the frequency of relapses and complications. This, they feel, is particularly important in patients treated with antibiotics, since, when the infection has been controlled by their use, the agglutinin titer does not rise. Stimulation of the formation of immune bodies by vaccination should, therefore, be of value, and in 3 patients with typhoid fever, they began vaccination 4 or 5 days after the temperature returned to normal, giving 3 injections at 6 or 7 days' interval. This brought about a satisfactory rise in the agglutination titer for typhoid and paratyphoid.

In a case of typhoid fever treated with chloramphenicol by Matteucci and co-workers,<sup>200</sup> the patient became afebrile and the blood cultures negative, but the stools continued to be positive for *S. typhosa*, after more than 30 days of treatment. Aureomycin was then substituted for the chloramphenicol and, after 8 days, stool cultures became permanently negative.

In a Panel Discussion on the treatment of diseases of internal medicine,<sup>228</sup> Maclochlán commented that, while typhoid responds astonishingly well to chloramphenicol, most cases treated with this antibiotic had relapses. In 2 out of the 4 patients seen by him, the bacillus returned to the blood stream.

In a study of 12 cases of typhoid fever, 8 with bacteremia,

treated with aureomycin, Yodh and Vakil<sup>325</sup> found that the drug had a beneficial, though variable, effect on the disease. Seven of the 8 cases with severe toxemia showed definite improvement in 48 to 72 hours. In 2 cases chloramphenicol had to be given to produce satisfactory response. In 3 cases blood cultures were sterile within 48 to 96 hours. A definitely favorable response was obtained in 41 per cent of the cases, and in no case was there any major complication. There was only 1 relapse, a rate of 8.5 per cent, which is much less than the incidence of relapse in chloramphenicol-treated cases and in untreated cases. The authors believe that the incidence of relapse might be lower if aureomycin and chloramphenicol were used in combination and are investigating this point, as well as the effect of aureomycin on the incidence of complications and of the carrier state.

Pflanz<sup>234</sup> gave aureomycin to a patient with typhoid fever. Temperatures were completely normal within 48 hours, but 3 weeks later the bacteria could still be cultured from the stool.

## *Typhus Fever*

Zinsser in his classic, "Rats, Lice and History,"<sup>328</sup> has traced the loss of wars, the collapse of empires, and great alterations in the course of history to the ravages of typhus fever. The control of rickettsial diseases by antibiotics has now removed at least one of the great causes for social upheaval and human misery.

*Epidemic Typhus*—Epidemic typhus fever, caused by *R. prowazekii* (including the recrudescence form, Brill's disease) has been repeatedly treated with aureomycin,<sup>20,233,263,318</sup> with rapid and complete clinical response. It is considered by Ruiz Sánchez<sup>257</sup> to be the drug of choice in exanthematous typhus. Benhamou and his group,<sup>16</sup> reporting similar results, state that the response of epidemic typhus to aureomycin is spectacular as regards the fever, but that other clinical signs regress more slowly than in murine typhus. For serious cases of epidemic typhus, these authors rec-

ommend an initial dose of 2 Gm. of aureomycin, followed by moderate dosage until the temperature is reduced, administration being continued at increased dosage intervals for an additional 3 or 4 days.

Cheng-Kai Fu,<sup>96</sup> in Kunming, China, where the treatment of typhus fever has always been a major therapeutic problem, has adopted the following regimen for this infection: 400 milligrams of aureomycin hourly for 3 doses, followed by 200 milligrams every 2 hours for 23 doses, the complete course of therapy lasting 48 hours. In 4 cases reported by him, the temperature became normal in 28 to 48 hours after beginning the drug. In every case there was a return of the patient's feeling of well-being within 24 hours. No complications occurred, and convalescence was very much shorter than usual. There was no relapse. These patients were treated on the sixth to eighth day of their disease, and neither the development of the skin eruption nor the development of a positive Weil-Felix reaction was interfered with.

In a typical case of typhus fever, reported by Timur,<sup>305</sup> aureomycin treatment was begun on the eleventh day and continued for 3½ days, to a total of 8 Gm. Within 12 hours the temperature was normal, and in 24 hours the patient appeared to be well. The patient was discharged on the eighteenth day. A blood specimen taken on the fifteenth day gave a negative Gruber-Widal reaction, but a positive Weil-Felix reaction. Timur remarks that until the discovery of aureomycin, which marked the beginning of the domination of rickettsial disease, the treatment of typhus fever was purely symptomatic. Sulfonamides and penicillin completely failed, and the use of convalescent serum and whole blood was of very doubtful value.

Cleave<sup>50</sup> has described a case occurring in Malta, in which the illness was at first described as a case of "pyrexia of unknown origin," since the symptoms and the rash were not at first typical of any specific fever, and blood tests were negative for Malta fever, typhoid and septicemia. Aureomycin was begun as a precautionary

measure, because of the great exhaustion of the patient. Response to aureomycin was prompt and the temperature fell rapidly to normal. The day after beginning aureomycin, the rash showed the typical characteristics of typhus fever. Three days later, the agglutination test against typhus was strongly positive. Convalescence was uneventful except for profound exhaustion.

In the differential diagnosis of poliocencephalitis, typhus fever may have to be considered. Pfeiffer<sup>233</sup> found a polymorphonuclear and lymphocytic increase in the spinal fluid of patients with murine or epidemic typhus. Aureomycin was very effective in controlling the infection.

de Magalhães and associates,<sup>77</sup> in Brazil, advocate the use of aureomycin in the treatment of exanthematous typhus, associated with chloramphenicol in severe cases, and aided by the use of supportive remedies such as heart tonics and diuretics.

Giroud<sup>106</sup> and co-workers describe an annual epidemic of exanthematous typhus in Oubangui, French Africa, which lasts for 4 months following the burning of underbrush to get rid of rodents. Usually, after a particular area has been burned over, cases of typhus develop 9 or 10 days later. It is assumed that the animals take refuge in local dwellings. The authors describe 4 cases in detail, and stress the remarkable therapeutic effect of aureomycin. In each of these cases, there was a history of malaria and, on the assumption that the existing attack was a malarial relapse, the patients were given quinine and other antimalarial drugs without effect. In all 4 patients, the temperature became normal within 48 hours of beginning aureomycin. Three of them remained afebrile, but the fourth patient had a return of fever several days after treatment was begun, and was discovered to have a malarial attack, with numerous parasites in the blood. Treatment with quinine was effective at this time and the patient recovered rapidly.

*Endemic (Murine)*—The results of aureomycin treatment in murine typhus, caused by *R. mooseri*, are similar to those obtained in Rocky Mountain spotted fever.

Woodward<sup>318</sup> has reported good response to aureomycin in 1 case, Cutileiro<sup>68</sup> in 2 cases, and Hill<sup>136</sup> in 8 cases of this infection. Knight, Ruiz Sánchez, Ruiz Sánchez and McDermott<sup>165</sup> gave aureomycin to 19 patients, with prompt reduction of temperature and complete recovery in all cases. Discomfort disappeared almost overnight. Dramatic improvement and prompt clinical remission were noted by them in a further series of cases,<sup>163</sup> and they conclude that aureomycin is highly effective in murine typhus. Ruiz Sánchez and Ruiz Sánchez<sup>258</sup> have remarked that the clinical picture returns almost to normal in the first 36 hours of aureomycin treatment and that the shortening of the course of the disease is proportional to the promptness with which therapy has been begun. Lopez Kruger and Peñarrieta,<sup>190</sup> using a total dose of only 4 or 5 Gm., obtained normal temperatures in 24 hours in 6 cases of endemic typhus, with excellent clinical response in every case.

A patient apparently suffering from recrudescant epidemic typhus has been reported by House<sup>139</sup> as responding to aureomycin, the temperature being normal on and after the tenth day of illness, and the third day of aureomycin treatment.

Giroud, Boyer and Vargues<sup>105</sup> believe that cases of latent rickettsial infection are not uncommon. They feel that energetic and prolonged treatment with effective antibiotics such as aureomycin should be given in all rickettsial diseases, and cite 13 cases of typhus fever (usually Brill's disease) in which the original infection had taken place some time previously; in several cases, many years before. Reference is made in the chapter on cardiovascular disease to a cardiac form of Brill's disease.

## *Varicella*

Although chickenpox is generally a mild disease, needing only symptomatic treatment, much discomfort is produced by the rash, and scarring may result. Aureomycin seems to be of benefit. However, patients have developed varicella in the course of aureo-



mycin therapy,<sup>25,98,214,272</sup> and Mazursky and co-workers<sup>203</sup> were unable to detect any effect from aureomycin in 41 cases of chickenpox, as compared with 41 controls.

Local application of aureomycin in a methylcellulose aqueous solution, which dries to form a protective film, was found by Kalz, Prichard and Surkis<sup>149</sup> to prevent the formation of fresh vesicles and to hasten the disappearance of existing lesions, without scarring. Reduction in toxicity and shortening of the course of the infection by systemic aureomycin have been observed by Lindberg,<sup>179</sup> who also observed rapid drying of the vesicles. Varicella pneumonia, a rare but very grave complication of chickenpox, has responded dramatically to aureomycin in 3 recorded cases.<sup>36,212</sup>

Further reports are awaited on the aureomycin treatment of this infection.

# CHAPTER NINE

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CONDITIONS IN WHICH THE ROLE OF  
AUREOMYCIN IS BEING INVESTIGATED

AUREOMYCIN is known to exert a beneficent influence on several conditions not obviously of bacterial or viral origin. Its mode of action is not clear, but it is probable that in most cases the effect is an indirect one, operating through an alteration of the intestinal flora.

*Blood Dyscrasias*

*Pernicious Anemia*—Lichtman and associates<sup>18</sup> found that, in pernicious anemia patients, 2 to 3 Gm. of aureomycin administered for a month or more caused the bone marrow to return to normal. The reticulocyte crisis was unpredictable, and the clinical response slower than that caused by liver extract or vitamin B<sub>12</sub>. Their findings suggest that aureomycin makes the essential hemopoietic factors more available to the pernicious anemia patient.

Karamchandani,<sup>17</sup> reviewing the problems presented by megaloblastic anemia, suggests that in this type of anemia, when it follows intestinal stenosis or the formation of intestinal loops containing stagnant material, there may be a change in the flora of the involved intestinal loop. This change may consist in the disappearance of some organism which synthesizes hemopoietic material, or the predominance of some organism which interferes with its absorption or utilization. The effect of oral aureomycin on such abnormal bacterial activity may explain its hemopoietic action in

this gastroenteric type of megaloblastic anemia.

Toon and Wangenstein<sup>36</sup> found that a macrocytic or normocytic anemia could be produced in the rat by the artificial formation of blind segments of intestine; local ulceration did not appear to be a major factor in causing this anemia. They found that aureomycin was potent in preventing this blood change and suggested, like Karamchandani, that unusual bacterial activity resulting from intestinal stasis might be a significant etiologic factor, and that the effect of aureomycin was to inhibit such bacterial hyperactivity. Animals fed aureomycin did not develop anemia following operation.

Barnard<sup>5</sup> believes that peptones arising from the proteolytic activity of the normal intestinal flora in an abnormally permeable intestinal tract may cause hemopoietic arrest. Small quantities of aureomycin, just sufficient to suppress the usual proteolytic intestinal flora and to substitute a saccharolytic, Gram-positive one (*S. faecalis* and *Lactobacillus*), have caused rapid clinical and hematological improvement in patients with hemolytic anemia. Barnard remarks that splenectomy may soon be outmoded for this condition.

Aaron<sup>1</sup> has reported a case of hemolytic anemia with icterus, occurring during the course of a viral pneumonia with a high cold-agglutinin titer. The patient was given penicillin, but 24 hours later aureomycin was added because of a rise in temperature to 102° F. By the fourth day, the temperature was normal and the patient felt well. The next day, jaundice had practically disappeared.

*Leukemia*—In a study of the chemotherapy of leukemia in adults, made by Wright and associates,<sup>37</sup> aureomycin was used on a number of occasions for its effect on secondary infection. In no case did it appear to have any effect on the underlying disease. Sturgis<sup>38</sup> recommends aureomycin in leukemia solely for the purpose of controlling secondary infection.

Plauchu and his associates<sup>28</sup> also believe that the effect of aureomycin in leukemia is to control secondary infection, for which purpose it seems more active than penicillin and has been effective in certain cases of failure with the latter antibiotic.

In a child with leukemia observed by Björkwall,<sup>10</sup> fever dropped somewhat after aureomycin was given. Penicillin seemed to have no effect. Aureomycin was discontinued after 4.5 Gm. had been given, because the patient would not take it, but shortly thereafter there was a remarkable increase in the white blood cells. The author feels that one cannot altogether disregard the role of aureomycin in this phenomenon.

Shwachman and Kennell<sup>31</sup> have referred to the effect of aureomycin on the course of a patient with acute leukemia. The patient suffered from multiple large abscesses caused by *Staph. albus*, and combined treatment with penicillin, streptomycin and a sulfonamide had failed. When these remedies were discontinued and oral aureomycin given, a striking improvement took place, followed by a complete hematologic and clinical remission lasting for almost a year.

*Thrombocytopenia*—Péringuey<sup>26</sup> has reported cases of thrombocytopenia and anemia, which responded dramatically to aureomycin after the failure of transfusions. The underlying disease in these cases was onyalaï, a form of thrombocytopenic purpura peculiar to the African negro. It is possible that in such cases the action of aureomycin was not purely an anti-infective action, although the mechanism is obscure. In these conditions, aureomycin may act to some extent as a vitamin, or as a growth factor, since a dietary deficiency or allergy seems to be present in many cases.

A young girl gravely ill with thrombocytopenic purpura of obscure etiology, entering the service of Jossérand and Garin,<sup>16</sup> was found to have a normal clotting time, a bleeding time of 15 minutes, and practically complete absence of platelets. An emergency blood transfusion was given and all of the classic anti-hemorrhagic remedies were administered. The patient had recurrent epistaxes, necessitating repeated transfusions. Because fever was present, aureomycin was given for 7 days. At the end of this time, the temperature was normal, the red count had risen, the bleeding time was 9 minutes, and the platelets numbered about

8,000. Except for 2 more attacks of epistaxis, requiring transfusion, the patient had no further difficulty. Since the hemorrhagic state had appeared in this girl shortly before the age of puberty, the authors believed that they might relieve it by hastening the onset of menstruation. They therefore administered hypophyscal extracts, gonadotropic hormone, and prolan for one month. For the 3 days before she was discharged from hospital, she received distilbenc. When seen 2 months later, the girl was menstruating apparently normally, and hematologic examination found blood values to be normal. In view of the fact that no change for the better occurred until aureomycin was given, it seemed probable that the purpura was produced by an infectious agent.

### *Effect on Growth*

In animals, aureomycin has been shown by a number of workers<sup>9, 11-15, 21, 24, 25, 32-34</sup> to have a stimulating action on growth.

Recent work by Meites<sup>22</sup> indicates that vitamin B<sub>12</sub> and aureomycin protect the thymus against the action of cortisone, and confirms the increased requirements for vitamin B<sub>12</sub> when large doses of cortisone are given. Depression of growth of the body, hair and thymus of young rats on a vitamin B<sub>12</sub>-deficient diet, given daily injections of cortisone, can be prevented in whole or in part by giving vitamin B<sub>12</sub> or aureomycin, the addition of either of these to the diet being accompanied by increased appetite and greater efficiency in converting food into flesh. Vitamin B<sub>12</sub> was rather more effective than aureomycin and the 2 combined were more effective than either alone.

Shwachman and associates<sup>30</sup> speak of the promotion of growth observed in children with pancreatic fibrosis treated with small amounts of aureomycin, but note that the improvement in such cases may be the result of control of complicating infection. The effect of aureomycin ingestion on the nitrogen metabolism of children with this disease has been discussed in Chapter IX.

Perrini<sup>27</sup> has observed the effect of aureomycin on the growth of 10 premature infants. The rate of growth was more rapid than that of controls. Augmentation of weight was observable on the seventh day and was very evident by the tenth.

Robinson<sup>29</sup> has studied the effect of aureomycin administration on the body weight of premature infants. For this study he used 11 sets of twins and 2 sets of triplets, giving the antibiotic to the weaker one of the twins, or the weakest one of the triplets, and reserving the stronger children as controls. The type of nursing care and the diet were identical, as a rule, in both groups. The duration of treatment varied between 12 and 28 days. All the babies who received aureomycin gained weight considerably more rapidly than did the controls, except in 2 cases when controls and treated baby gained the same amount. The average daily gain was 29.5 Gm. in the treated group and 18 Gm. in the controls. All the infants who received a full course of aureomycin lived; 5 of the 15 controls died from intercurrent infection.

At this time Barnard<sup>6-8</sup> has under observation a series of patients who have been taking a small daily dose of one of the streptomycetes-derived antibiotics (streptomycin, aureomycin). Observations were begun after observing the increased appetite and unusually rapid growth of children receiving aureomycin for upper respiratory infections. An interesting observation has been that certain chronic alcoholics voluntarily curtailed their drinking or stopped entirely while taking the antibiotic. They appeared to have completely lost their taste for alcohol.

## *Neoplasms*

Ayre<sup>3</sup> has reported apparently complete regression of 6 anaplastic lesions of the cervix, in a series of 13 cases, following the direct topical application of aureomycin. No effect on these lesions had been produced with estrogens or progesterone, either alone or combined with penicillin or streptomycin. Ayre<sup>4</sup> suggests that this

type of cancer may be of infectious origin. He does not claim that aureomycin is a cure for cancer. No invasive cancer showed regression, even when treated early.

The original observations which prompted Ayre's use of aureomycin in cancer were those of MacLean,<sup>19</sup> who found that in a number of cases of precancer or cancer of the cervix, there was a 65 per cent incidence of infection with *Trichomonas vaginalis*. Local applications of aureomycin were used for the vaginitis, and routine cytologic examinations showed that the inflammation of the cervix and hyperactive nuclear changes of the cells of the cervical epithelium became less marked. He therefore investigated the action of aureomycin in a precancerous condition of the cervix coincident with early pregnancy. Two months after treatment was begun, the patient aborted and curettage was performed 3 weeks later. Two weeks postoperatively, smears showed complete disappearance of the possibly precancerous, or inflammatory, type of cell. MacLean notes that it is not possible to say definitely whether the reversion toward normal resulted from the aureomycin treatment or from the removal of the products of gestation, but believes that the vaginal administration of aureomycin was a factor in this change, since abnormal cells were still present after all tests for pregnancy had become negative. It was only later, after continued aureomycin treatment, that the cytologic picture became normal.

An observation which seems to favor the virus hypothesis of the origin of cancer is that when cortisone was given to mice with virus tumors, the tumors regressed for varying periods of time, but the mice soon died of recurrence. On the other hand, when aureomycin was given as well as cortisone, the tumor regressed completely and the mouse lived its normal life span. These observations led to the trial of similar treatment in cases of human cancer. Maguire and McElhone<sup>20</sup> have treated a series of cases of advanced malignant disease with aureomycin and ACTH. Sixteen patients have been treated, and 15 are still under treatment. All of



these patients had inoperable cancers, confirmed by biopsy. All patients, except for 1 with a very advanced cancer who died in the second week of treatment, have improved. One man is again taking part in some of the routine work of his law practice and 4 others are going home on maintenance doses. All of the others when treatment was begun were weak, bedridden and suffering pain; they are now comfortable, feeling well and ambulatory. Aureomycin is given in the amount of 2 Gm. daily (twice this amount in very advanced cases) and ACTH is given on a graded schedule for a 15-day course, followed by a maintenance dose of 10 to 40 mg. a day. The authors believe that larger doses can be given for longer periods and that the indication for reducing the dose is intolerance on the part of the patient. All of the patients are kept on a low salt diet. On this therapy, fluid retention was apparent during the first week but shortly thereafter, after pronounced diuresis, edema disappeared for good. After this episode the patients gained weight steadily. In every case the patient regained his appetite within a few days, vomiting ceased and, in about 2 weeks, he was eating everything that was set before him. The authors do not claim cure for any of these patients. In the 5 patients whose case histories are given, the original growth was still present and unaltered in size or appearance, except for 2 cases in which it showed some shrinkage.

Antikajian, Wright, Plummer and Weintraub<sup>2</sup> have noted an inhibitory effect of aureomycin *in vitro* on the total fibroblast outgrowth from human lymphatic neoplasms (lymphosarcoma).

Moreau and co-workers<sup>23</sup> have used aureomycin in the treatment of 22 cases of infected cancer. Eighteen were definitely improved. Aureomycin exerts a constant effect on the fever and on the general condition. The temperature begins to drop often as early as the first evening after beginning treatment. In tumors which are easily observed directly, rapid cleaning of the lesion has been seen and the fetid odor disappears. The sedimentation rate clearly indicates control of the infection.

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